Synthesis and Utilization of Guanidine Catalysts for Applications Directed Towards the Preparation of Butenolide and Modified Amino Acid Derivatives

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Abstract

Development of guanidine catalysts is explored through direct iminium chloride and amine coupling, alongside a 2-chloro-1,3-dimethyl-1H-imidazol-3-ium chloride (DMC) induced thiourea cyclization. Synthesized achiral catalyst *N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl) aniline proved unsuccessful towards *O*-acyl migrations, however successfully catalyzed the vinylogous aldol reaction between dichloro furanone and benzaldehyde. Incorporating chirality into the guanidine catalyst utilizing a (*R*)-phenylalaninol auxiliary, generating (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol, demonstrated enantioselectivity for a variety of adducts. Highest enantiomeric excess (ee) was afforded between dibromofuranone and *p*-chlorobenzaldehyde, affording the *syn* conformation in 96% ee and the *anti* in 54% ee, with an overall yield of 30%. Attempts to increase asymmetric induction were focused on incorporation of axial chirality to the (*R*)-phenylalaninol catalyst using binaphthyl diamine. Incorporation of (*S*)-binaphthyl exhibited destructive selectivity, whereas incorporation of (*R*)-binaphthyl demonstrated no effects on enantioselectivity. Current studies are being directed towards identifying the catalytic properties of asymmetric induction with further studies are being aimed towards increasing enantioselectivity by increasing backbone steric bulk.

Acknowledgements

I would like to take this opportunity to thank my supervisor, Dr. Travis Dudding for his guidance and patience with me. Without his advice I would most likely still be stuck somewhere in the midst of this thesis, diligently working away.

A great deal of thanks also goes out to my fellow graduate students and lab mates, especially to the former members of Dr. Costa Metallinos' group Dr. Josh Zaifmen, Shufen Xu and Lori Van Belle. They were always there to offer their best advice when I had any questions regarding experimental techniques or theory.

This work has helped me grow as an individual and demonstrated that things don't always work the way you would think, but with enough effort and patience it is almost always possible to find a solution.

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I. Introduction

I-1. Natural Products

On a molecular level, our bodies reveal an array of chemical reactions responsible for maintaining health and integrity. Involved in these reactions is the innate ability of biological systems to distinguish the correct substrates for specific pathways. Not only must these substrates possess the correct functional groups for binding, but groups must be arranged in the correct regions, often requiring the correct asymmetry. Compounds without an internal plane of symmetry are referred to as asymmetric or chiral. They are enantiomers if they exist as non-superimposable mirror images of each other. These properties are exploited in metabolic processes, as demonstrated by the occurrence of asymmetric amino acids that primarily occur as the L-enantiomer in species such as mammals. Furthermore, these asymmetric compounds have important consequences to pharmaceutical industries.

Pharmaceuticals are often prepared from symmetric, achiral, chemical reagents incapable of distinguishing enantiomers, resulting in a mixture of products, termed a racemate. Most often only one of structures is correctly recognized by an active site, while the other enantiomer has two fates. It can either be harmless; eventually being degraded and making the drug 50% efficient, or it can react with different receptors causing undesired side effects. As a result, the biggest area of chemical research lies in asymmetric synthesis, referring to the stereoselective synthesis of chiral compounds.

In relation to this work, focus is directed towards butenolide containing natural products, in addition to synthetic peptides, specifically with modifications at the α-carbon.

I-1.1. Butenolides

Interest in butenolide compounds stems from the numerous butenolide containing natural products that have been identified. Butenolides are four carbon cyclic esters and fall into the class of lactones. They exhibit biological activities involving antibiotic[37], antitumor[40] and cytotoxic properties.[25] They also function as inhibitors of biosynthetic pathways.[31] Interest lies in development of synthetic methods for facile construction of derivatives of butenolide natural products, such as tetronasin, Figure I-1 .[34]

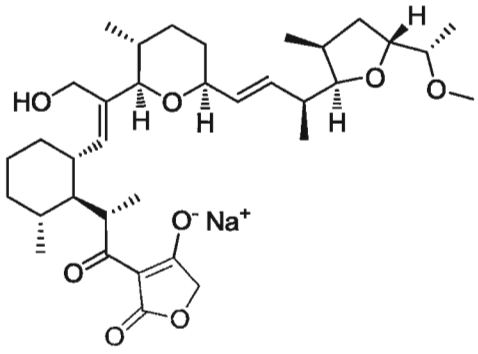
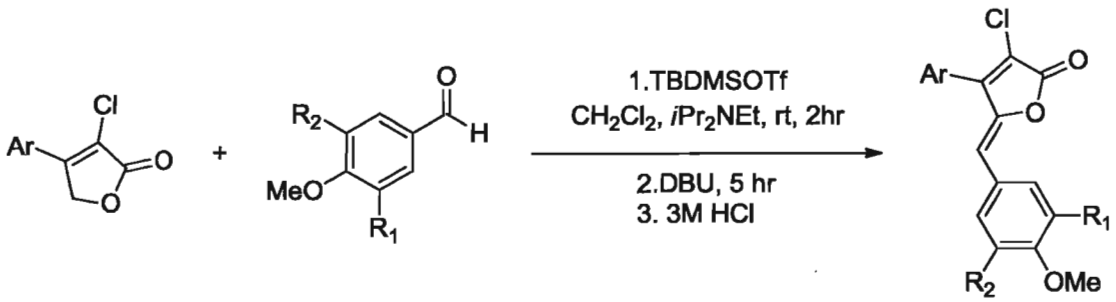


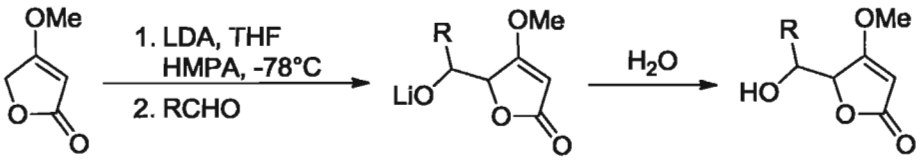
Figure I-1: Tetronasin, a butenolide (outlined in red) containing natural product.

One group of derivatives is butenolides with substituents at the γ-position, which refer to substitutions at the methylene position of the butenolide in Figure I-1 . Such derivatives have previously been prepared through γ-substitution of aryl aldehydes into butenolide derivatives, yielding γ-alkenes, Scheme I-1.[3]



Scheme I-1: γ-Substitution of aryl aldehydes into butenolide derivatives

Another potential approach, of more importance to this work, lies in the vinylogous aldol reaction, Scheme I-2. It provides access to functionalized δ-hydroxy carbonyl compounds containing a double bond.[6]



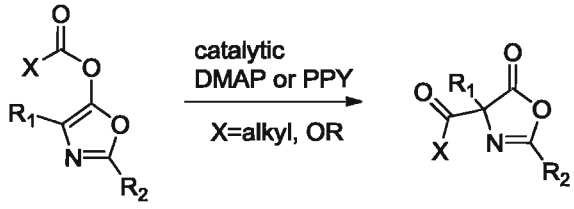
Scheme I-2: Vinylogous aldol approach to γ-substituted butenolides

I-1.2. Modified Peptides

In addition to butenolides, there is also interest in generating modified α-amino acids, which play an important role in drug discovery and understanding biological phenomena.[49] These amino acids possess modifications at the α-carbon, forming quaternary α-centers. This has the potential to introduce conformational constraints for optimal binding conformations, enhancing biological activity and potentially metabolic stability. As a result, the synthesis of α-substituted amino acids has attracted substantial attention.[49]

One potential method of achieving such derivatives is the *O*-acylated azalactone rearrangements. These have been reported using 4-(dimethylamino)pyridine (DMAP) and

4-(pyrrolidino)pyridine (PPY), Scheme I-3, generating new carbon-carbon bonding and quaternary centers. Since azalactones are more reactive, they provide selectivity that can be used towards preparation of α-alkylated amino acids.[46]



Scheme I-3: *O*-acylated azalactone rearrangement using DMAP or PPY

Additionally, these rearrangements have also been accomplished using a chiral pyridine derivative, Figure I-2.[52]

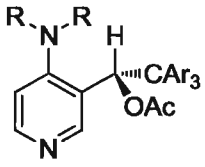


Figure I-2: Chiral pyridine derivative also used for *O*-acylated azalactone rearrangement

I-2. Guanidines

In an approach towards synthesis of modified butenolide compounds, discussed in section I-1.1.1, and modified modified α-amino acids, section I-1.1.2, this work utilizes guanidine catalysis towards achieving asymmetric product formation. The properties and chemistry of the guanidine moiety will be introduced next, with a brief overview of guanidine functionality in natural products and synthetic chemistry.

I-2.1. Guanidines – Properties and Chemistry

The guanidine moiety presents itself in numerous naturally occurring products. It consists of a carbon bound to three nitrogen atoms. Guanidines can exist in three canonical forms, allowing for increased stabilization of their protonated guanidinium form, illustrated in Figure I-3. As a result, they possess a high pKa, approximately 12.5, allowing them to act as superbases and remain protonated over a wide pH range, including those of physiological conditions.[33] This leads to their characteristic function in biological activity, discussed below.

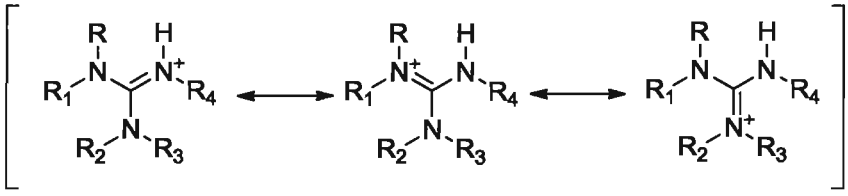


Figure I-3: Resonance structures of a guanidine moiety

I-2.2. Guanidine Containing Natural Products

Guanidines are prominent throughout nature and have been identified in many naturally occurring products. The most prominent of which is the amino acid L-arginine, Figure I-4. Arginine acts as an important substrate for living organisms, such as being an important metabolite that leads to the formation of creatine, which holds an important role in energy metabolism of muscle and nerve tissues.[54]

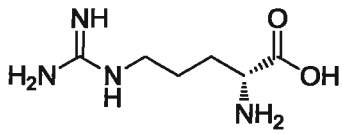


Figure I-4: L-Arginine – guanidine containing amino acid

Guanidines are also found in more complex compounds, originating from terrestrial, marine and freshwater microorganisms, terrestrial and marine invertebrates, marine sponges and higher plants.[4] They possess significant biological activity; displaying a variety of pharmacological properties including antifungal, antiviral and anti-HIV properties.[4] Marine natural products have always been of significant interest. They possess biologically and pharmaceutically important substances and typically have chemically unique structures, rarely found in terrestrial metabolites.[27] A classic example of such a product is ptilomycalin A, illustrated in Figure I-5, from the Caribbean sponge *Ptilocaulis spiculifer*.[26] This guanidine-containing substance was found to have significant cytotoxic activity against numerous cancer cell lines and against the DNA polymerase of Human immunodeficiency virus type 1 reverse transcriptase.

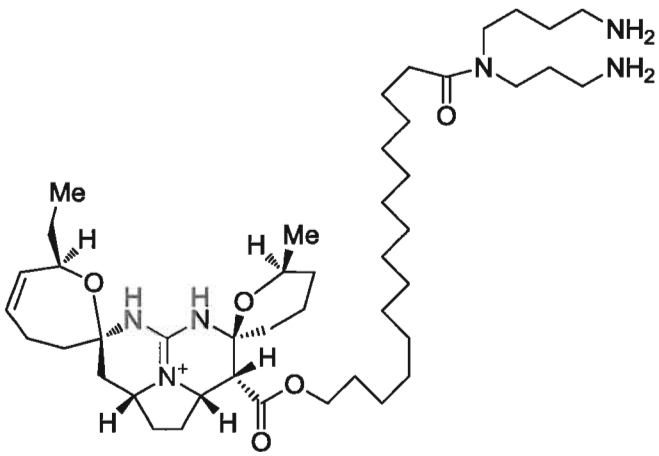


Figure I-5: Ptilomycalin A.

Additionally, guanidines play an important part in structure and functionality of biological proteins and processes including enzymatic catalysis, further discussed below.

I-2.3. Guanidines in Enzyme Catalysis

The aforementioned chemical properties of the guanidine moiety allows for the guanidine sidechain of arginine to hold various roles in enzymes. Guanidines remain protonated over a wide pH range, including those of physiological conditions, giving them an associated cationic character. Therefore, they are frequently found in enzymes whose ligands or cofactors contain anionic groups including nucleotide bases, phosphates and carboxylates,[57] as seen in the active site of L-arginine: glycine amidinotransferase, Figure I-6.[16] Within this active site, the protonated side chain of L-arginine residue, Arg322, coordinates to the carboxylate end of an L-arginine substrate.[16] It helps orientate and tether L-arginine for transfer of an amidino group to glycine, producing L-ornithine and guanidinoacetic acid.[16]

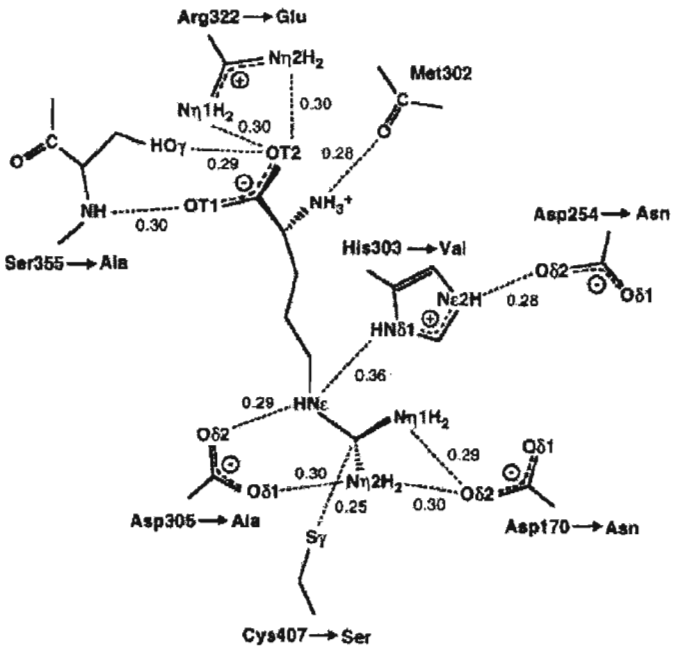


Figure I-6: L-arginine 322 coordination of an L-arginine substrate.[16]

Guanidines are generally poor candidates for general bases in enzymatic catalysis because they typical exist in protonated states in physiological conditions.[14] However, arginine has been found to operate as a general base for the enzyme catalysts IMP dehydrogenase, fumarate reductase, pectate/pectin lyases and L-aspartate oxidase.[14] This action is possible because these enzyme active sites possess residues that perturb the local pKa environments, allowing arginine to remain neutral, illustrated for pectate/pectin lyase in Figure I-7. [14]

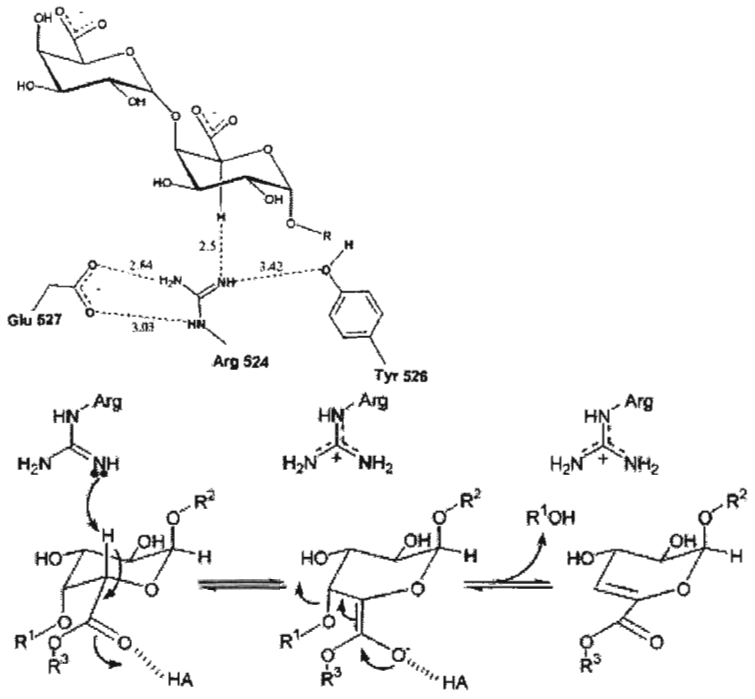


Figure I-7: Arginine involved in pectate/pectin lyase.[14]

As mentioned, guanidines play numerous roles in enzymatic catalysis, however, the basicity of the guanidine moiety is that which appeals most to chemists and leads to the growing interesting in development and utilization of novel guanidines as superbases in chemical catalysis.

I-2.4. Guanidines in Organic Synthesis

Numerous nitrogen containing compounds are classified as organic bases; they include amines, amidines and guanidines. Of these, guanidines are the strongest bases because of the resonance stabilization of their conjugate acids, as depicted in Figure I-3.[20]

Additionally, in comparison to other organic bases, guandines provide easy access to a wide variety of molecular modifications; theoretically, five different chiral ligands can be introduced to the nitrogen atoms, as illustrated in Figure I-8. Hence, guanidines can play important roles in asymmetric catalysis.

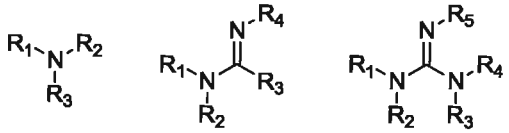


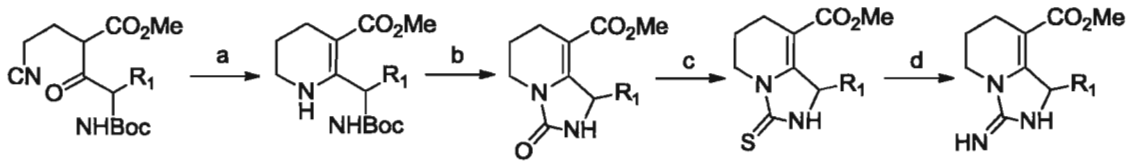
Figure I-8: Illustration of possible locations for ligand incorporation on different nitrogen species.

I-2.4.1. Preparation Methods/Synthesis

The exploitation of the basic properties of guanidines has been limited due to difficulties in preparation of complex guanidine structures.[17] However, numerous preparation methods have recently been developed allowing for exploration of guanidine containing catalysts in synthetic chemistry. The various methods of guanidine preparation are discussed below.

I-2.4.1.1. Classic Preparation Method

One of the first methods for the preparation of guanidines involves the reaction of thiourea with ammonia at elevated temperatures in the presence of lead (II) chloride.[9] Knowledge of such conversions led to the possibility of prepare various guanidines through simple transformations, as long as the thiourea derivatives were obtainable, as shown with work by Rao et al., Scheme I-4.[42] However, despite offering complex guanidines, these methods were harsh and did not allow access to a variation of guanidine substituents.



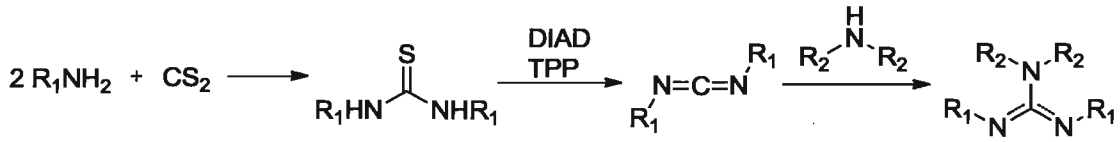
Scheme I-4: a) Raney-Nickel, H_2, EtOH, 70 °C, 70 psi, 2 hr. b) HCl, Ether, rt, 2 hr. c) Triphosgene, pyridine, DCM, rt, 4 hr. d) Lawesson's reagent, dioxane, reflux, 12 hr. d) $NH_3AgSO_3CF_3$, DCM, -10°C -rt, 5hr.

Eventually, guanidine preparation evolved into methods capable of generating complex guanidines, allowing for easy manipulation of *N*-substituents, helping tap into their unexplored potential in asymmetric catalysis. Synthesis of these more complex guanidines was achieved through various pathways, which will be briefly discussed.

I-2.4.1.2. Synthesis of C_2 Symmetric Guanidines

The generation of C_2 symmetric guanidine derivatives was achieved by Chinchilla et al., as outline in Scheme I-5.[7] This involved the preparation of guanidines starting from thioureas, obtained by reacting two equivalents of a primary amine with carbon disulfide.[7] Subsequent desulfurization of the thioureas was achieved using diisopropyl

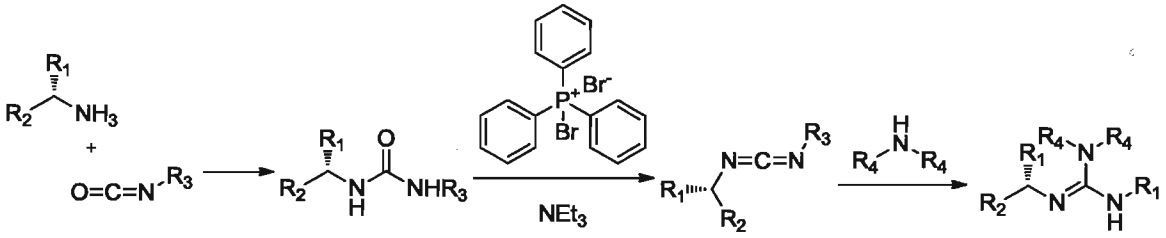
azodicarboxylate (DIAD) and triphenylphosphine, to afford homochiral carbodiimides, which were then reacted with a secondary amine, to yield C_2 symmetric guanidines.[7]



Scheme I-5: Pathway for C_2-symmetric guanidine derivatives.

I-2.4.1.3. Synthesis of Homochiral Guanidines

A similar procedure for the synthesis of homochiral guanidines by the same authors is outlined in Scheme I-6.[7] Primary amines were reacted with isocyanates to afford the corresponding ureas. Dehydration of the urea using bromotriphenylphosphonium bromide and triethylamine led to generation of carbodiimides, which were then reacted with secondary diamines, yielding the desired guanidines.

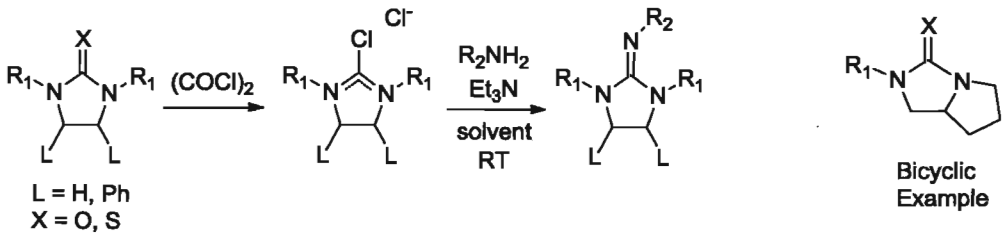


Scheme I-6: Generation of homochiral guanidines.

I-2.4.1.4. Synthesis of Cyclic Guanidines

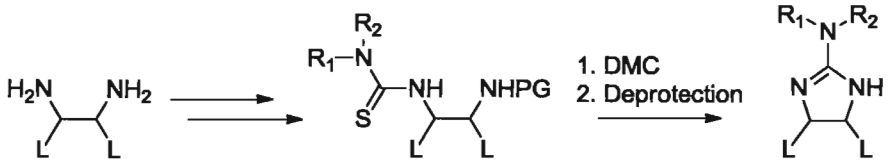
The first method of preparing cyclic guanidines uses diamines as starting materials, as outlined in Scheme I-7.[17] The diamines are converted to ureas and then into their corresponding iminium chlorides, which are then coupled to various primary amines.[17]

Additionally, this method is also viable for generation of bicyclic compounds from cyclic diamine precursors, also shown in Scheme I-7.



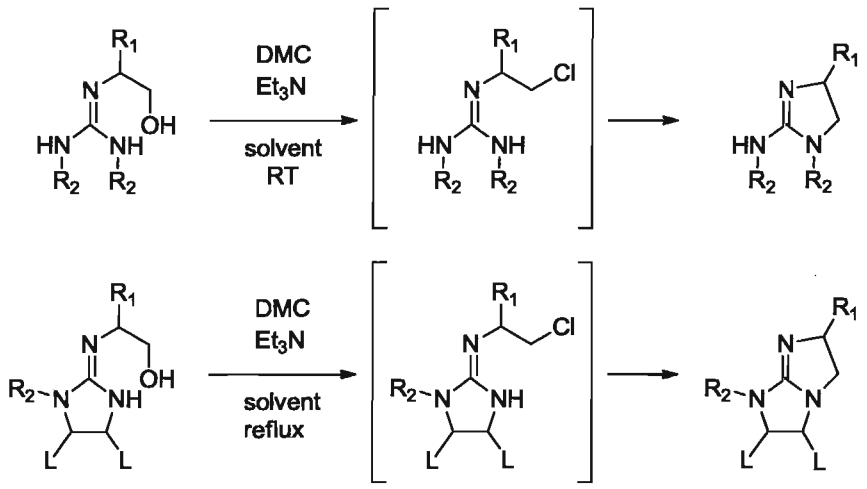
Scheme I-7: Cyclic guanidine formation through iminium chloride and amine coupling.

The second method focuses on cyclic urea formation by cyclization of protected thioureas, derived from ethylene diamines, utilizing 2-chloro-1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium chloride (DMC), Scheme I-8.[20] This method can utilize either trisubstituted or disubstituted thioureas to yield corresponding guanidines.



Scheme I-8: Cyclic guanidine formation through thiourea cyclization.

The third method involves transformation of simple guanidines into more complex structures. It again employs the use of DMC induced cyclization, however this approach uses hydroxyethyl functionalized guanidines. Simple chlorination of the hydroxyl allows for subsequent cyclization and is shown in Scheme I-9.[20] This method is employed to introduce a cyclic nature to linear guanidines. Alternatively, it can be employed to introduce a bicyclic structure into pre-existing monocyclic guanidines.[20]



Scheme I-9: Cyclization of guanidines with hydroxyethyl functionality.

The development of numerous synthetic methods for generating chiral guanidines, discussed above, has expanded their uses as organic catalysts.

I-2.4.2. Use as solution based Chiral Guanidine Catalysts

I-2.4.2.1. Henry Reaction

To date, guanidines play an important role in organic synthesis and have been used for catalysis of various enantioselective reactions, including the Henry reaction.[7] The Henry reaction is a classical carbon-carbon bond forming reaction between a nitroalkene and an aldehyde, discovered in 1895.[41] The discovery of the strong ionic interaction formed between a bicyclic guanidine and nitroalkenes, illustrated in Figure I-9, led to the identification of good potential models for asymmetric catalysts for the Henry reaction.[5]

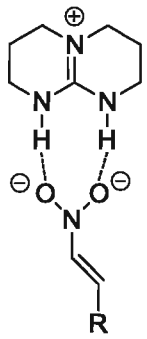
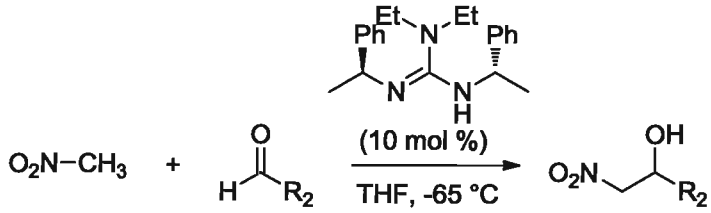


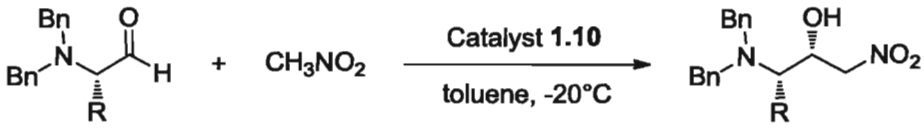
Figure I-9: Ion-pairing between a bicyclic guanidine and a nitroalkene.

In 1994, the first asymmetric catalysis of the Henry reaction, utilizing a guanidine catalyst, was reported by Najera and coworkers.[7] After investigation of several guanidine catalysts, the C_2-symmetric catalyst shown in Scheme I-10, achieved the highest enantioselectivity, affording products with an enantiomeric excess (ee) up to 54%.[7]



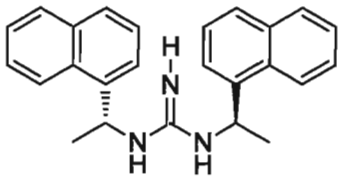
Scheme I-10: Henry reaction of aldehydes and nitromethane.

Expanding on the Henry reaction, guanidines were explored for their potential as catalysts of diastereoselective reactions (d.r) between *N,N*-dibenzyl α-amino aldehydes and nitromethane, Scheme I-11.[36]



Scheme I-11: Diastereoselective Henry reaction of nitromethane with *N,N*-dibenzyl α-amino aldehydes.

Catalyst 1.10, illustrated in Figure I-10, was similar to that used by Najera, however, it took advantage of more bulky substituents, affording ee's of 92% in the best scenarios.



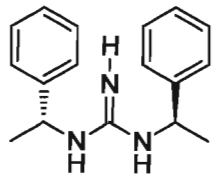
1.10

Figure I-10: Catalyst 1.10: 1,3-bis((*R*)-1-(naphthalen-1-yl)ethyl)guanidine.

I-2.4.2.2. Michael Addition

Further reviewing guanidine catalysts, there have been numerous reports of guanidine catalyzed Michael additions.[33] The Michael addition is a common approach to carbon-carbon and carbon-halogen bond formation and involves the conjugate addition of a nucleophile to electron-deficient alkenes.[1] Michael reactions provide a good overview of the structurally different guanidine catalysts, spanning from linear, to cyclic, to polycyclic and to axial chiral.

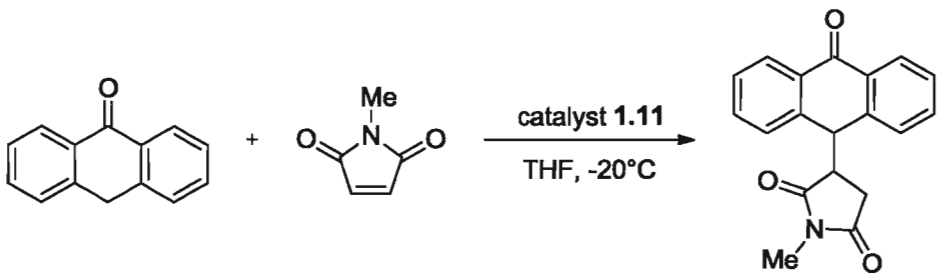
Ma and coworkers, employed a C_2-symmetric linear catalyst, illustrated in Figure I-11, similar to their catalyst for the Henry reaction (Scheme I-10) for Michael addition of anthrone and *N*-methylmaleimide, Scheme I-12.[35,36]



1.11

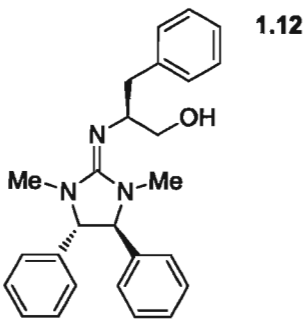
Figure I-11: 1,3-bis((*R*)-1-phenylethyl)guanidine.

No conclusive work has been performed to determine the reaction mechanism; however, product was obtained in 67% yield and 77% ee.



Scheme I-12: Michael addition of anthrone and *N*-methylmaleimide.

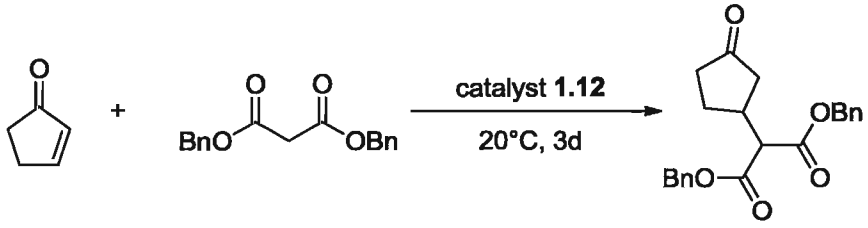
Cyclic guanidines have also proven useful in Michael reactions. Ishikawa and coworkers, demonstrated the effectiveness of chiral guanidine catalysts in reactions of glycinate with various Michael acceptors.[19] Their best catalysts, illustrated in Figure I-12, afforded high yields with a highest ee of 97%.



1.12

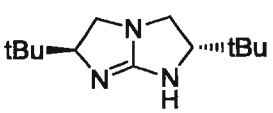
Figure I-12: (*S*)-2-(((4*S*,5*S*)-1,3-dimethyl-4,5-diphenylimidazolidin-2-ylidene)amino)-3-phenylpropan-1-ol.

Additionally, Ishikawa and coworkers found the same guanidine to successfully catalyze the reaction of 2-cyclopenten-1-one and dibenzyl malonate, Scheme I-13.[32] However, the highest ee they obtained was 43%, with a yield of 65%. Despite this, they successfully demonstrated the potential of guanidine catalyst application towards an array of chemical transformations.



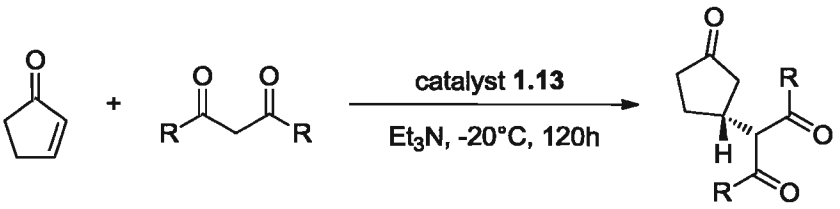
Scheme I-13: Reaction of 2-cyclopenten-1-one and dibenzyl malonate.

Further expanding on the diversity of guanidine compounds, Tan and coworkers employed a bicyclic guanidine illustrated in Figure I-13, and used it for the catalysis of 2-cyclopenten-1-one with various 1,3-dicarbonyl compounds, Scheme I-14.[58] They were able to drastically improve on the results obtained by Ishikawa et al., achieving excellent yields with most ees greater than 90%.



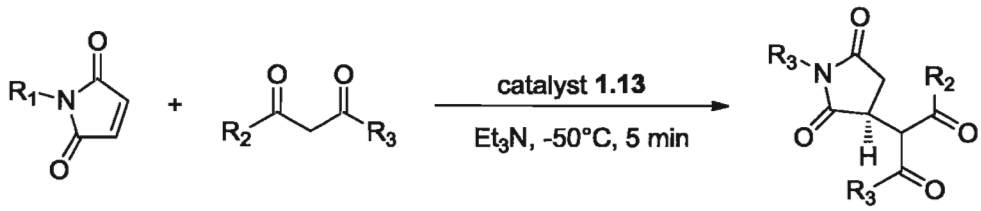
1.13

Figure I-13: Example of a bicyclic guandine.



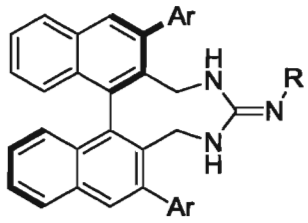
Scheme I-14: Catalysis of 2-cyclopenten-1-one with various 1,3-dicarbonyl compounds.

The applicability of this bicyclic catalyst was also expanded to incorporated maleimides as Michael acceptors, Scheme I-15.[24]



Scheme I-15: Maleimide reactions with 1,3-dicarbonyl compounds.

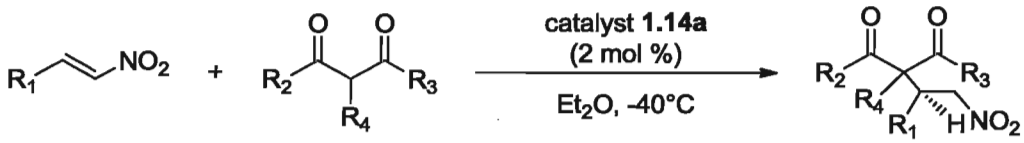
In addition to the previously discussed acyclic and cyclic guanidines, are guanidine catalysts possessing an axial chiral backbone. Axial chirality acts as an excellent approach to steering enantioselective reactions, demonstrated by Terada et al., with their incorporation of a binaphthyl backbone, Figure I-14.[47]



1.14a: Ar = 3,5-(3,5-di-*t*BuC$_6$H$_3$)2C$_6$H$_3$, R = Me
1.14b: Ar = 3,5-di-*t*BuC$_6$H$_3$, R = Bn

Figure I-14: Guanidine catalyst with axial chiral backbone.[47]

Incorporation of axial chirality with attached 3,3'-aryl appendages, showed remarkable increases in selectivity towards Michael additions between dimethyl malonate and a variety of aromatic nitrokalkenes, Scheme I-16. The reactions proceeded with high yields and enantioselectivities, with a highest yield of 99% and 98% ee.[47]

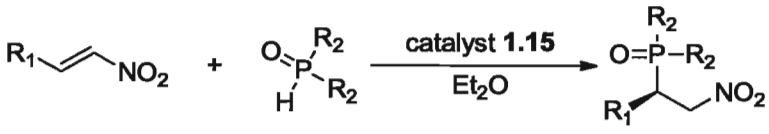


Scheme I-16: Michael additions between dimethyl malonate and nitroalkenes.

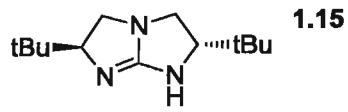
However, as with every reaction, limitations were exhibited. Reaction ee's were greatly influenced by malonate bulkiness, with decreasing ee's coccuring as the steric bulk increased. Additionally, aromatic nitroalkenes were more reactive, while aliphatic derivatives required more catalyst and longer reaction times.[47] Having described the roles of numerous guanidines in the evolution of enantioselective Michael additions, phospho and oxa- Michael reactions will now be addressed.

I-2.4.2.3. Phospha-Michael Reaction

Chiral α-amino and β-amino phosphonic acids function as analogues to amino acids. Although numerous methods exist for the enantioselective preparation of α-amino phosphonic acids, not many exist for the β derivatives.[11] Tan et al. reported catalysis of the phospha-Michael reaction of conjugated aryl nitroalkenes with diaryl phosphine oxides, Scheme I-17, using a chiral bicyclic guanidine, Figure I-15. Excellent enantioselectivities, enhanced by recrystallization, were obtained with di-(1-naphthyl) phosphine oxide and various nitroalkenes using 10 mol % catalyst loading.[11]



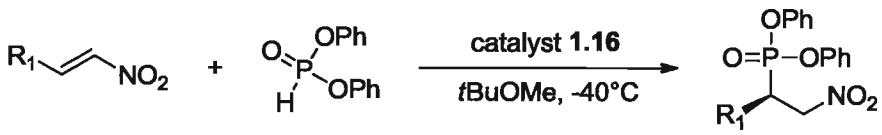
Scheme I-17: Reaction of conjugated aryl nitroalkenes with diaryl phosphine oxides.



1.15

Figure I-15: Chiral bicyclic guanidine.[11]

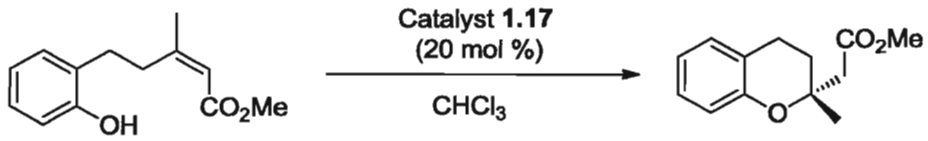
Looking at a related phospha-Michael reaction, the potential for variability in guanidine catalysts of similar reactions is clearly demonstrated. The catalysts illustrated in Figure I-14 and Figure I-15, are remarkably different, yet they catalyze closely related reactions, seen by comparing Scheme I-17 to Scheme I-18. Additionally, this demonstrates that use of an axial chiral guanidine shows improvement in enantioselectivities, with a best result being 97%.[48]



Scheme I-18: Catalysis of diphenyl phosphite to nitroalkenes.

I-2.4.2.4. Oxa-Michael Reactions

To further demonstrate the applicability of guanidine catalysts, oxa-Michael reactions are addressed. They can be used in the formation of oxygen containing heterocycles, forming chromanes and flavanes, present in numerous natural products, such as vitamin E.[44] Ishikawa et al. recently explored the potential of intramolecular oxa-Michael cyclizations of phenol derivatives as an entry to chiral chromanes, Scheme I-19.[44] Using a chiral guanidine catalyst, depicted in Figure I-16, they were able to obtain enantioselectivities of 76% with yield of 83%.[44] These results demonstrate the effectiveness of guanidine catalysts in this field.



Scheme I-19: Oxa-Michael cyclizations of phenol derivatives.

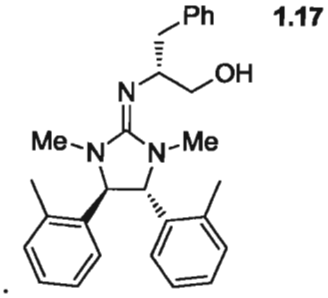
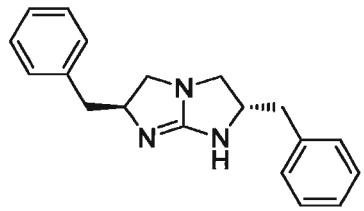


Figure I-16: Chiral guanidine catalyst for Scheme I-19.

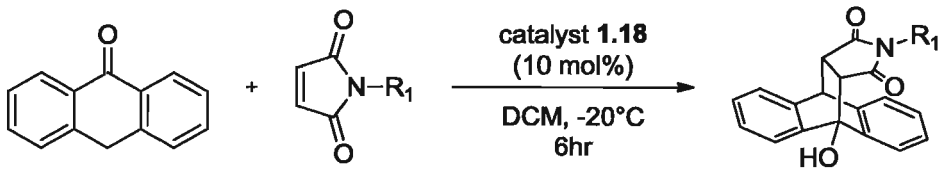
I-2.4.2.5. [4+2] Cycloadditions

Guanidines have also been employed as catalysts for enantioselective [4+2] cycloadditions, also known as Diels-Alder reactions. However, as opposed to more the commonly explored Lewis acid catalyzed cycloadditions, guanidines are involved in asymmetric base catalyzed Diels-Alder reactions. These guanidines, an example of which is illustrated in Figure I-17, function as Brønsted bases activating dienes to give higher HOMO energies, opposed to lowering LUMO energies of the dieneophile in Lewis acid activation. For example, guanidines have been shown to catalyze the Diels-Alder reaction of anthrone with activated olefins, outlined in Scheme I-20, with many examples exhibiting high yields and ees greater than 98%.[45]



1.18

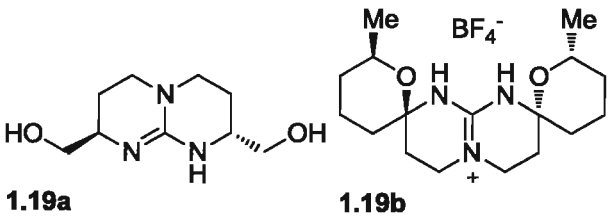
Figure I-17: Bronsted base guanidine catalyst for Diels-Alder reactions.



Scheme I-20: Diels-Alder reaction of anthrone with activated olefins.

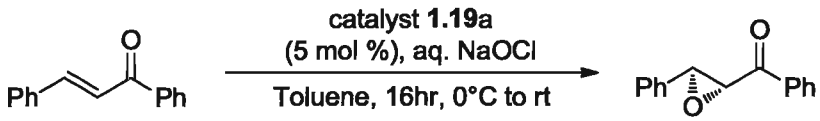
I-2.4.2.6. Nucleophilic Epoxidation Reaction

Chiral guanidines have also been investigated as chiral catalysts for nucleophilic epoxidation reaction.[12] Cyclic guanidines, illustrated in Figure I-18a, used in stoichiometric amounts were found to give respectable results, however, utilizing guanidinium salts, illustrated in Figure I-18b, provided better yields and enantioselectivities (99%, 93% respectively) for chalcone epoxidations, Scheme I-21.[15]



1.19a **1.19b**

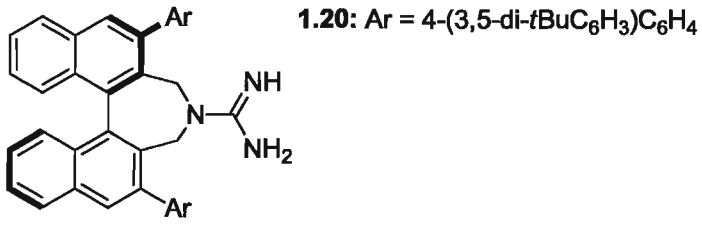
Figure I-18: a) Cyclic guanidine for epoxidations. b) Guanidinium salt for epoxidations.



Scheme I-21: Chalcone epoxidations using catalysts in Figure I-18.

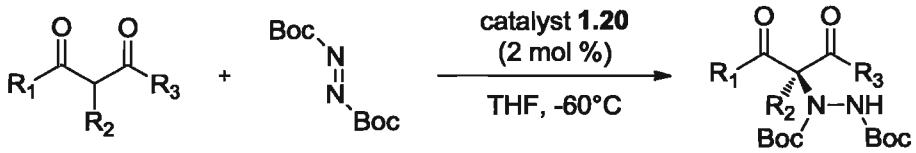
I-2.4.2.7. Electrophilic Amination Reactions

Further investigating the use of guanidine catalysts, axially chiral guanidine illustrated in Figure I-19, functioned well as catalysts for asymmetric electrophilic aminations. Reactions were performed with 1,3-dicarbonyl compounds using di-*tert*-butyl azodicarboxylate, outlined in Scheme I-22, whose bulkiness was crucial for enantioselectivity. Reactions were carried out affording excellent ees.[47]



1.20: Ar = 4-(3,5-di-*t*BuC$_6$H$_3$)C$_6$H$_4$

Figure I-19: Axial chiral guanidine for electrophilic amination.

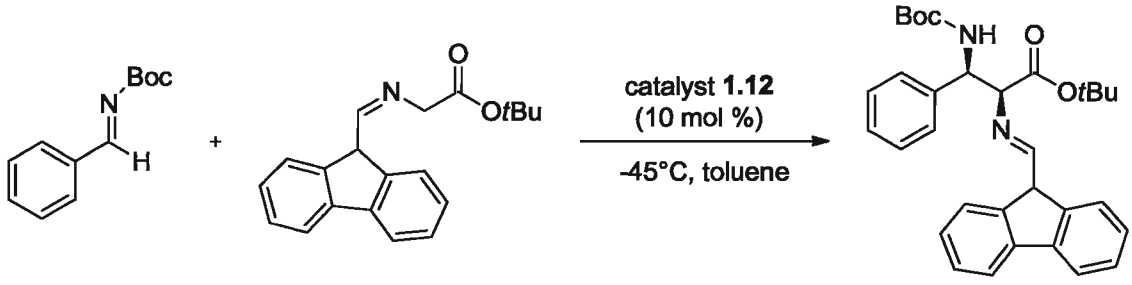


Scheme I-22: Amination of 1,3-dicarbonyl compounds with di-tert-butyl azodicarboxylate.

I-2.4.2.8. Mannich Reactions

Guanidines have also been shown to act as catalysts for Mannich reactions, a reaction used for converting imines to chiral β-amino carbonyls.[53] Previously mentioned

guanidine **1.12**, illustrated in Figure I-12, was shown to also catalyze the Mannich reaction of *N*-Boc protected imines to α,β-diamino esters, outlined in Scheme I-23.[28] These reactions help demonstrate the flexibility of guanidine catalysts towards a variety of reactions.



Scheme I-23: Mannich reaction of *N*-Boc protected imines to α,β-diamino esters.

I-2.4.2.9. Strecker Reaction

Another classic reaction for which guanidines have been employed to attain high enantioselective reactions is the Strecker reaction, shown in Scheme I-24. First reported in 1850, it is an excellent method for the synthesis of α-amino acids.[13] Lipton et al., reported a cyclic dipeptide guanidine catalyst, illustrated in Figure I-20, to afford good to excellent enantioselectivities with *N*-benzhydryl imines.[23]

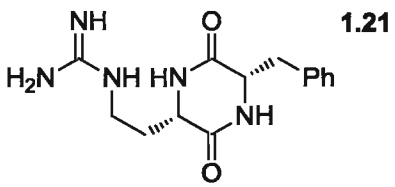
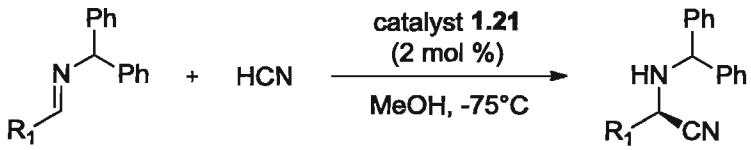
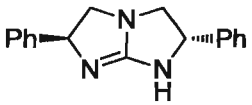


Figure I-20: Cyclic dipeptide guanidine catalyst.



Scheme I-24: Synthesis of α-amino acids with *N*-benzhydryl imines.

Moreover, Corey et al., applied a bicyclic guanidine **1.21**, illustrated in Figure I-21, to the Strecker synthesis, showing improvements over the dipeptide catalyst in reactions of aliphatic imines.[8]

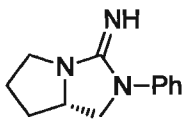


1.22

Figure I-21: Bicyclic guanidine used for strecker synthesis.

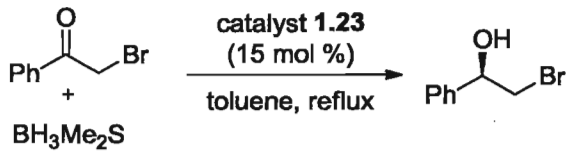
I-2.4.2.10. Reduction Reactions

Continuing the investigation of guanidine catalyzed reactions, Basavaiah et al, reported chiral guanidines, illustrated in Figure I-22, showing enantioselective catalysis of borane mediated reductions, such as those of phenacyl bromide, outlined in Scheme I-25.[2] The reaction yielded greater enantioselectivity under refluxing conditions then room temperature, with increases seen from 37% to 83%.[2]



1.23

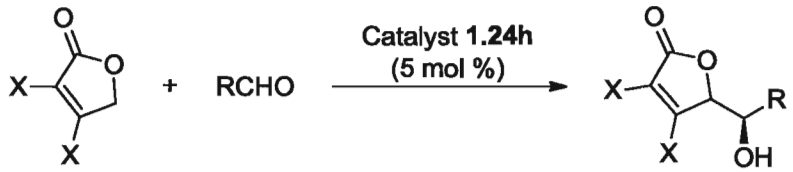
Figure I-22: Guandine catalyst for borane reductions.



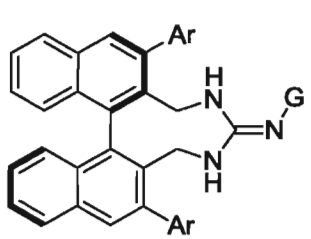
Scheme I-25: Catalysis of borane mediated reduction of phenacyl bromide.

I-2.4.2.11. Vinylogous Aldol Reactions

The vinylogous aldol reaction is a classic carbon-carbon bond forming reaction providing hydroxyl functionalized compounds containing a double bond, Scheme I-26. One of the most recently reported guanidine catalyzed asymmetric reactions is the vinylogous aldol reaction.[51] Ube et al. reported good yields with diastereotopic selection favouring *syn* over *anti* conformations, (90:10) with an enantiomeric excess of 99% with their best catalyst **1.24h**, illustrated in Figure I-23.



Scheme I-26: Vinylogous aldol reaction of aldehydes with butenolide.

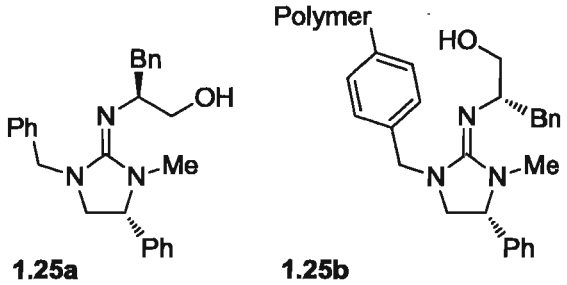


1.24a: Ar = Ph, G = CH_3
1.24b: Ar = Ph, G = PH_2CH
1.24c: Ar = 3,5-tBu$_2$C$_6$H$_3$,Ph, G = PH_2CH
1.24d: Ar = Ph, G = (3,5-Me$_2$C$_6$H$_3$)$_2$CH
1.24e: Ar = Ph, G = (3,5-(CF$_3$)$_2$C$_6$H$_3$)$_2$CH
1.24f: Ar = Ph, G = (4-MeOC$_6$H$_4$)$_2$CH
1.24g: Ar = Ph, G = (3,5-(MeO)$_2$C$_6$H$_3$)$_2$CH
1.24h: Ar = Ph, G = (3,4,5-(MeO)$_3$C$_6$H$_2$)$_2$CH

Figure I-23: Axial chiral guanidine catalyst for Vinylogous Aldol reactions.

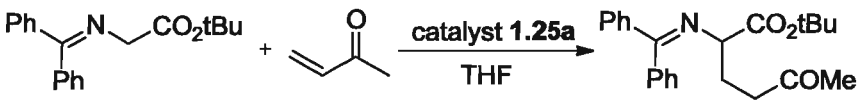
I-2.4.3. Solid Phase Chiral Guanidine Catalysts

Opposed to classic solution based organic catalyst, solid phase reagents offer various advantages, including easier scale-up operations and reusability. The use of chiral guanidines in this field is limited; however, Ishikawa et al. have synthesized a polymeric form of a previous solution based catalyst.[32]



1.25a **1.25b**

Figure I-24: a) Free Form Catalyst. b) Immobilized Polymeric Guanidine.



Scheme I-27: Michael Reaction of Glycinate.

The solution based catalyst **1.25a**, Figure I-24, afforded 74% ee of the Michael reaction product of glycinate, Scheme I-27 , however, despite their structural similarities; the polymeric guanidine, Figure I-24b, only afforded the product in moderate yields, with lower ee's of 45%.[32] The inactivity of such guanidines is most likely a result of the inaccessibility of the embedded catalyst, and more work needs to be done for development of efficient solid phase guanidine catalysts.[32]

I-2.4.4. Coordination by Chiral Guandine Ligands

In addition to solid phase, chiral guanidines are being utilized in other synthetic applications, such as metal ligands. Guanidine coordination has proven successful with metals such as zinc(II), illustrated in Figure I-25 and molybdenum.[29] Preliminary work has been focused towards the previously described Henry reaction, illustrated in Scheme I-10. However, despite showing successful catalysis, enantioselectivity was negligible.[29]

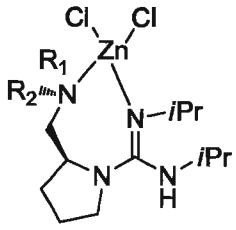


Figure I-25: Guanidine coordination to zinc.

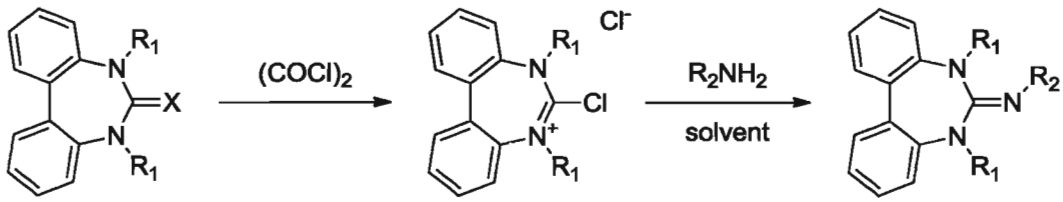
The use of guanidine catalysts to numerous synthetic reactions, as shown above, demonstrates their impact and future potential towards synthetic chemistry. The application of these catalysts in natural product synthesis is promising as they allow for greener chemistry, avoiding metal catalysis and harsh reaction conditions.

I-3. Focus

The focus of this work involves exploration of different synthetic routes for preparing polycyclic guanidine catalysts, possessing a 7-membered guanidine ring and an aromatic backbone. Focus will then shift towards utilization of synthesized guanidine catalysts for generating modified butenolide compounds and α-amino acids, helping provide entry into new routes for development of natural products composed of such derivatives.

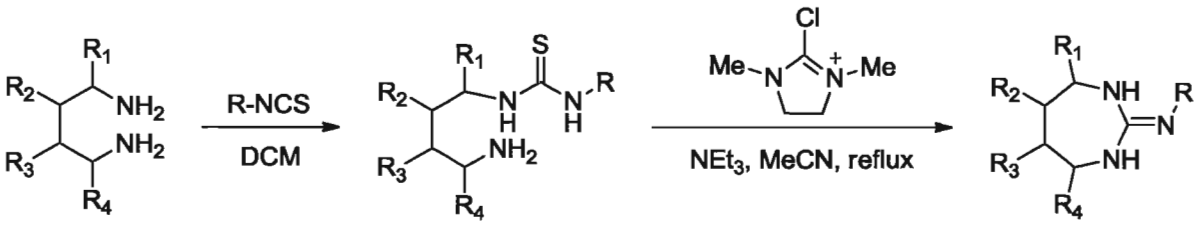
I-3.1. Catalyst Synthesis

Two synthetic routes will be mainly explored for the generation of such catalysts. The first will focus on generation of iminium chlorides from urea or thiourea precursors, and subsequent reactions with primary amines to afford the desired guanidines, Scheme I-28. This scheme shows promise for efficient access to a multitude of catalysts with varying auxiliaries.



Scheme I-28 : Guanidine generation through chloroiminium and amine coupling

The second potential method for guanidine synthesis is based on the formulation of thioureas, through reactions with isothiocyanates and diamines, followed by their subsequent cyclization to yield corresponding guanidines, outlined in Scheme I-29.



Scheme I-29 : Guanidine formation through thiourea addition and DMC induced cyclization.

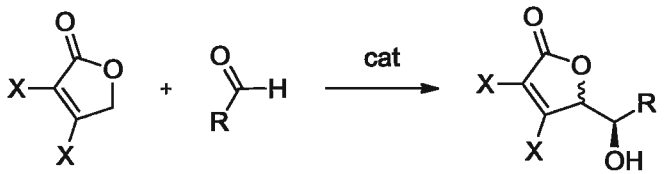
Upon successful generation of such guanidine species, their potential for catalysis and furthermore, asymmetric induction of reactions applicable to the synthesis of desired

natural products will be assessed and explored. In particular, reactions pertaining to synthesis of butenolide units and synthetic peptides are of interest.

I-3.2. Guandine utilization towards γ-substituted butenolide derivatives

In relation to butenolide derivatives, this work focuses mainly on γ-substituted butenolides and the generation of enantioselective derivatives through direct vinylogous aldol reactions. To date, there are very limited enantioselective reports of direct vinylogous aldol reactions, giving much appeal to this area. To allow entry into this field, use of 2-furanone derivatives as vinylogous nucleophiles will be utilized, as they are the simplest forms of butenolide compounds.

Moreover, dihalofuran-2(5H)-ones will be utilized, Scheme I-30. Interest in these particular furanones exists because halo substituents enhance the acidity at of the γ positioned hydrogens, allowing greater reactivity. At the same time, halo substituents also block the α-postion from bond formation.[51]

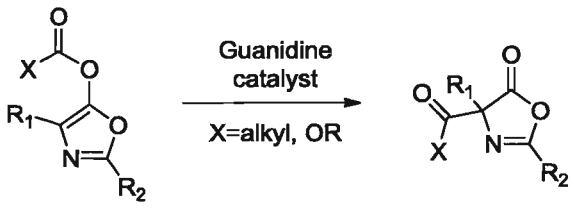


Scheme I-30: Vinylogous aldol reaction utilizing dihalofuran-2(5H)-ones.

I-3.3. Modified α-Amino acid synthesis through *O*-acyl migrations

Lastly, interest lies in generation of modified α-amino acids through *O*-acyl migrations. This method possesses tremendous potential towards stereoselective preparation of α-alkylated amino acids. Additionally, interest also lies in the area because current

reactions, described in section I-1.1.2, utilize nitrogen base catalysts, sparking the exploration of guanidine use in this field. Work will focus on attempting *O*-acyl migrations using synthesized guanidines, outlined in Scheme I-31.



Scheme I-31: *O*-acyl migration

II. Results and Discussion

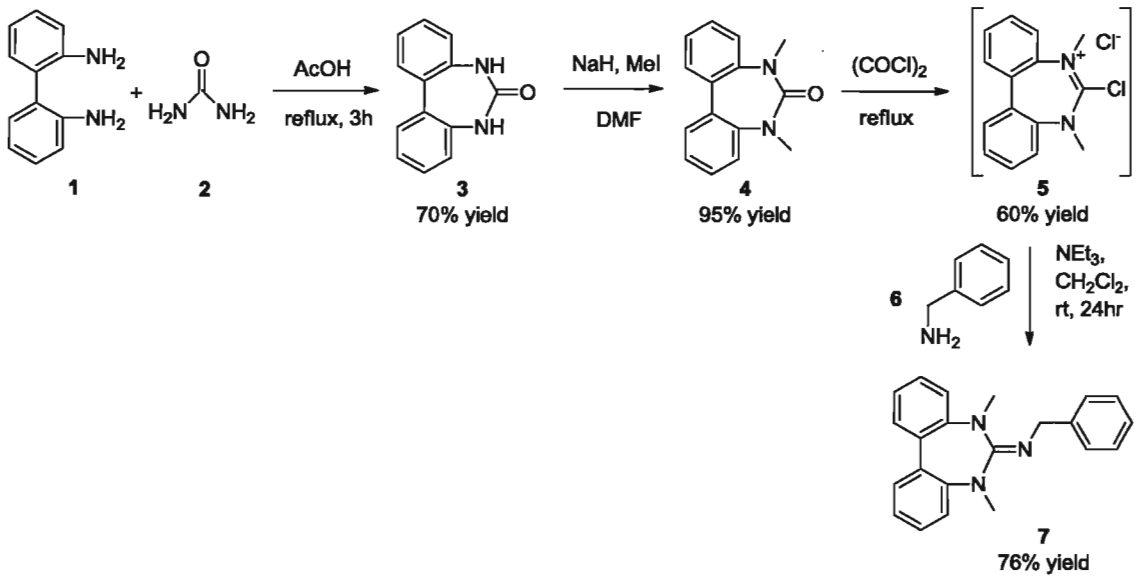
II-1. Synthesis of Guanidine Catalysts

II-1.1. Approaches Utilizing Iminium Chloride and Amine Coupling

Work towards the synthesis of chiral guanidine catalysts began with the reaction of iminium chlorides with primary amines, as described in Scheme I-28. As noted, the successful implementation of this route has great potential for the efficient synthesis of numerous guanidines possessing various auxiliaries, that sharing a similar backbone structure.

Investigation of this reaction began with the generation of a simple achiral guanidine. *N*-(5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-1-phenylmethanamine. **7** was prepared from 2,2'-diaminobiphenyl, **1**, and benzyl amine, **2**, in 4 steps, as outlined in Scheme II-1. The initial step involved the transformation of 2,2'-diaminobiphenyl into its corresponding urea **3**, using the methodology of Niementowski.[39] Formation of the urea introduced the required carbon linkage seen between the free amines of the guanidine product. The goal was now to substitute the carbonyl with an amine species. However, prior to the amination, activation of the urea carbonyl was required. To accomplish this, **3** was *N*-methylated using methyl iodide. This helped prevent formation of stable resonance species and helped protect the *N*-positions in successive reactions. Alkylation of these positions using other species is discussed below, Scheme II-3. Following alkylation, **4**, was converted into the highly reactive 6-chloro-5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-7-ium chloride, **5**, by chlorination using oxalyl chloride, following procedures similar to those previously reported by Ishikawa et al.[17]

Chlorination was found to be most successful in the absence of solvent and excess oxalyl chloride. The iminium chloride species was then aminated with achiral benzyl amine, **6**, affording the desired product, **7**.



Scheme II-1: Synthetic towards access to guanidines using iminium chlorides.

Generation of achiral guanidine **7** demonstrated the ease with which various auxiliaries could be integrated into the synthetic approach that allowed for the preparation of chiral guanidines. At that stage, work was directed towards the development of two novel chiral guanidine catalysts, **8** and **9**, each possessing the optically active (*R*)-phenylalaninol auxiliary, which has shown to possess good enantioselective induction in other works.[19,44,51] In addition to exploring the effect of a phenylalaninol auxiliary, the effects of utilizing bulky nitrogen substituents, such as *N*-protecting groups, on asymmetric catalysis was also investigated.

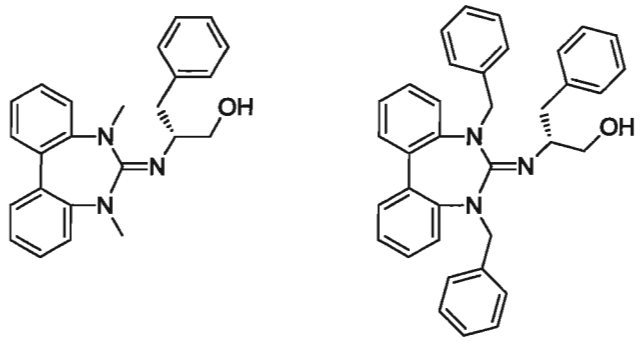


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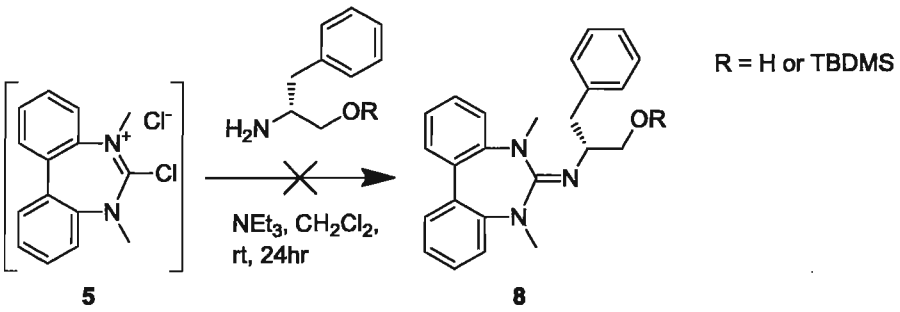
Figure II-1: (*R*)-phenylalaninol guandine catalysts with varying *N*-protecting groups

The first attempt at synthesis of (*R*)-2-((5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol, **8,** was performed, Scheme II-2, through an amination of the iminium chloride species, **5**, generated using Scheme II-1, with phenylalaninol. However, numerous attempts at product isolation and identification, using extractions and chromatography, proved unsuccessful. This was most likely attributed to the polar properties of the hydroxyl functionality, resulting in difficulties in isolation. Therefore, in an attempt to increase the ease of product isolation, we protected the hydroxyl functional group of the (*R*)-phenylalaninol with *tert*-butyldimethylsilyl (TBDMS), thereby reducing its hydrogen bonding character and possibly averting possible side reaction. Unfortunately, difficulties in product isolation after amination with TBDMS protected (D)-phenylalaninol were still encountered. More investigation into this reaction is warranted. In tandem with this work, generation of guanidine catalyst **9** was also being explored.



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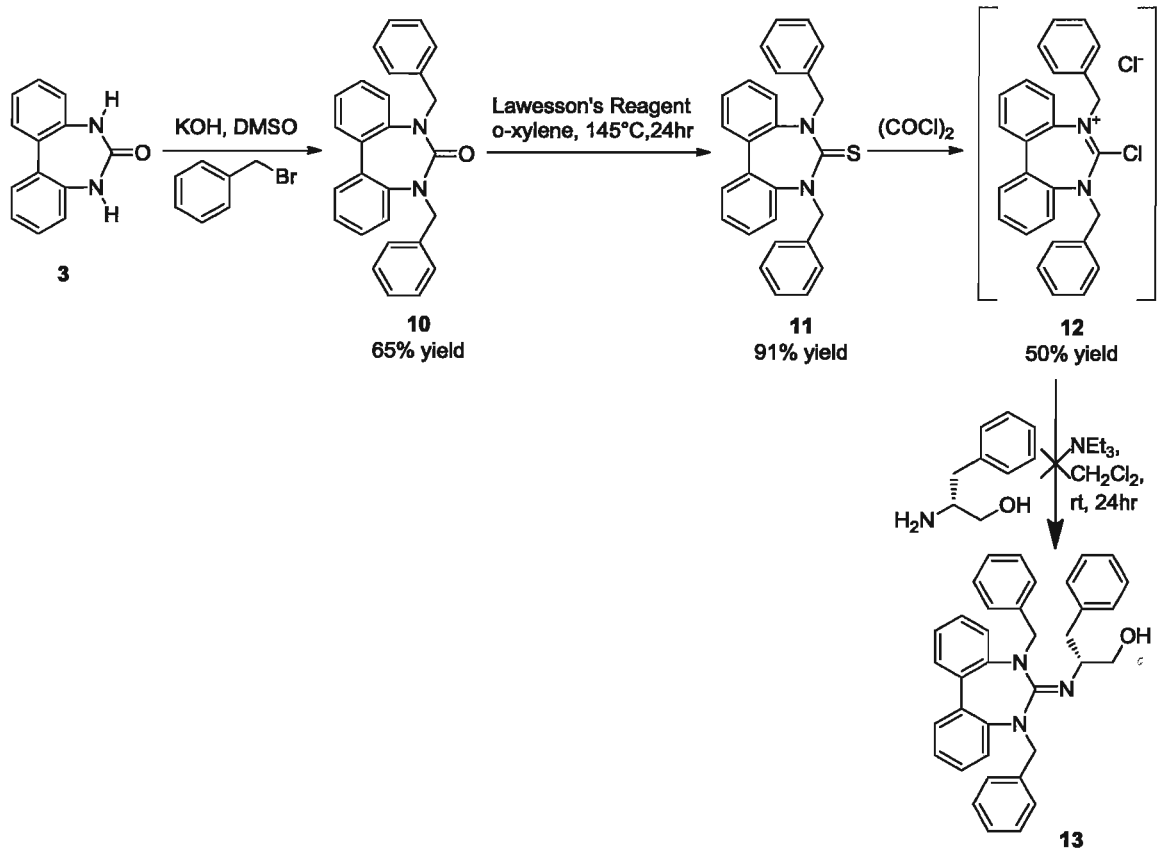
Scheme II-2: Chloroiminium coupling with protected and unprotected (*R*)-phenylananinol.

Recent work using imidazolidine rings found that the incorporation of bulky substituents has positive effects on asymmetric induction and additionally, increases the rate of catalytic turnover.[43] Therefore, alongside the aforementioned work, attempts to synthesize (*R*)-2-((5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol, **9**, were made, Scheme II-3. The synthetic pathway follows that of Scheme II-1, with a few modifications. First, in place of *N*-methyl substituents, benzyl groups were incorporated. *N*-benzylation of 5H-dibenzo[d,f][1,3]diazepin-6(7H)-one was accomplished using benzyl bromide, affording 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-one, **10**, according to the literature procedure by Kostyanovsky.[30] Additionally, conversion into the corresponding iminium chloride **12** failed with oxalyl chloride. This was a result of the unreactive nature of benzyl substituted ureas, as reported by Ishikawa et al.[43] In order to increase reactivity of the urea, **10** was converted into the corresponding thiourea, **11**, using Lawesson's reagent, following a procedure reported by Ishikawa et al.[43] Substitution of the urea oxygen, with the larger, more reactive sulfur atom successfully allowed for direct chlorination previously employed using oxalyl chloride. Unfortunately, attempts at amination with (*R*)-phenylalaninol presented the same problems previously encountered with the *N*-

methylated species. After numerous attempts at isolation through chromatographic methods and reported extractions on similar compounds,[19] other preparation methods of this guanidine were explored.

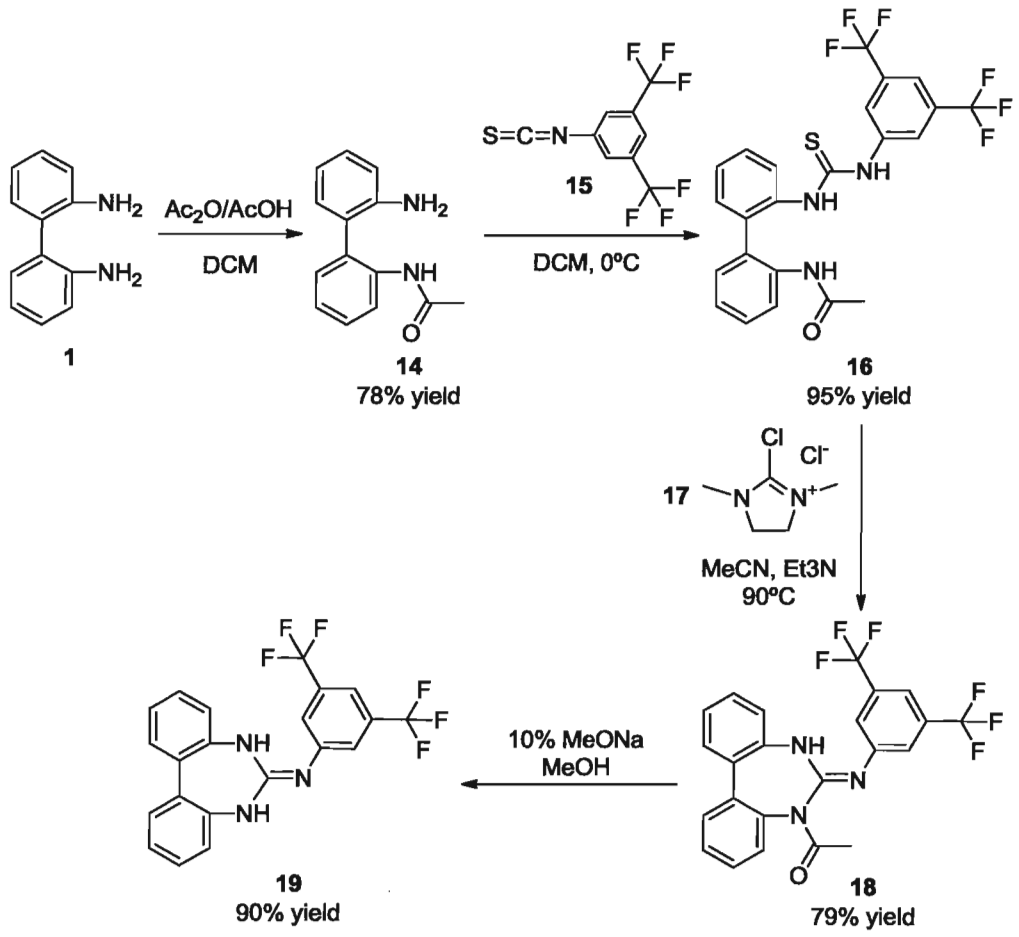


Scheme II-3: Preparation of *N*-benzyl substituted urea's and coupling with (*R*)-Phenylalaninol.

II-1.2. Approaches Utilizing DMC-Induced Thiourea Cyclization

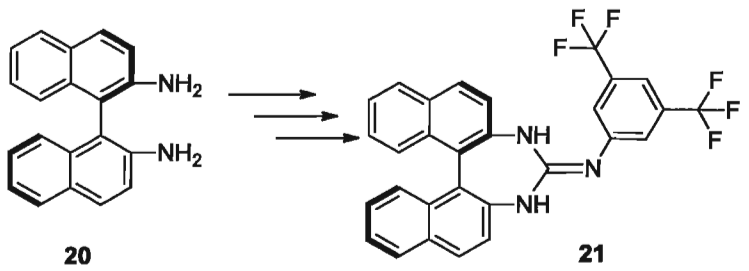
With failures in guanidine formation utilizing the previous methods described up to this point, our efforts focused next on guanidine preparation utilizing DMC-induced thiourea cyclization, Scheme I-29. This work began with the preparation of the 7-membered guanidine, initially possessing an achiral backbone.

In this vein, targeted *N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl)aniline, **19**, was prepared via the four step synthesis, as outlined in Scheme II-4. The synthesis began with the mono acylation of [1,1'-biphenyl]-2,2'-diamine, **1**, following a protocol established by Wang and coworkers, which afforded the protected acetamide species **14**.[55] To prevent formation of a bisacylated species, it was necessary to carry out the reaction under acidic reaction conditions, reducing the nucleophilic nature of the binaphthyl amines and making mono-acylation more favourable. Additionally, using 1 molar equivalent of acetic anhydride resulted in small amounts of bisacylation, therefore, an equivalence of 0.95 was used. The resulting monoacylated biphenyl species *N*-(2'-amino-[1,1'-biphenyl]-2-yl)acetamide, **14**, was converted into a biphenylamine thiourea (N-(2'-(3-(3,5-bis(trifluoromethyl)phenyl) thioureido)-[1,1'-biphenyl]-2-yl)acetamide), **16,** with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene, **15**, using methodology by Wang and coworkers[1]. Afterwards, a protocol by Ishikawa and coworkers was used to generate the thiourea derivative **18** by using 2-chloro-1,3-dimethylimidazolinium chloride (DMC), **17**. DMC induced cyclization of the acetamide nitrogen with the thiocarbonyl, thereby forming the imidazolidine ring system of reaction product 1-(6-((3,5-bis(trifluoromethyl)phenyl) imino)-6,7-dihydro-5H-dibenzo[d,f][1,3]diazepin-5-yl)ethanone. Lastly, the acyl protecting group was removed by treatment with base reducing the acetamide back to its native form, giving the final product, *N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl)aniline, **19**.



Scheme II-4: Synthetic route of the four step DMC-induced guandine formation.

Upon successful utilization of this route towards guanidine preparation, a test synthesis was conducted utilizing (*S*)-(-)-1,1'-binaphthyl-2,2'-diamine, **20**, checking the ability to incorporate axial chirality using the protocol outlined in Scheme II-4. Catalyst preparation was successful for preparing **21** from **20**. More attention to this axial chiral concept is given later in this work.



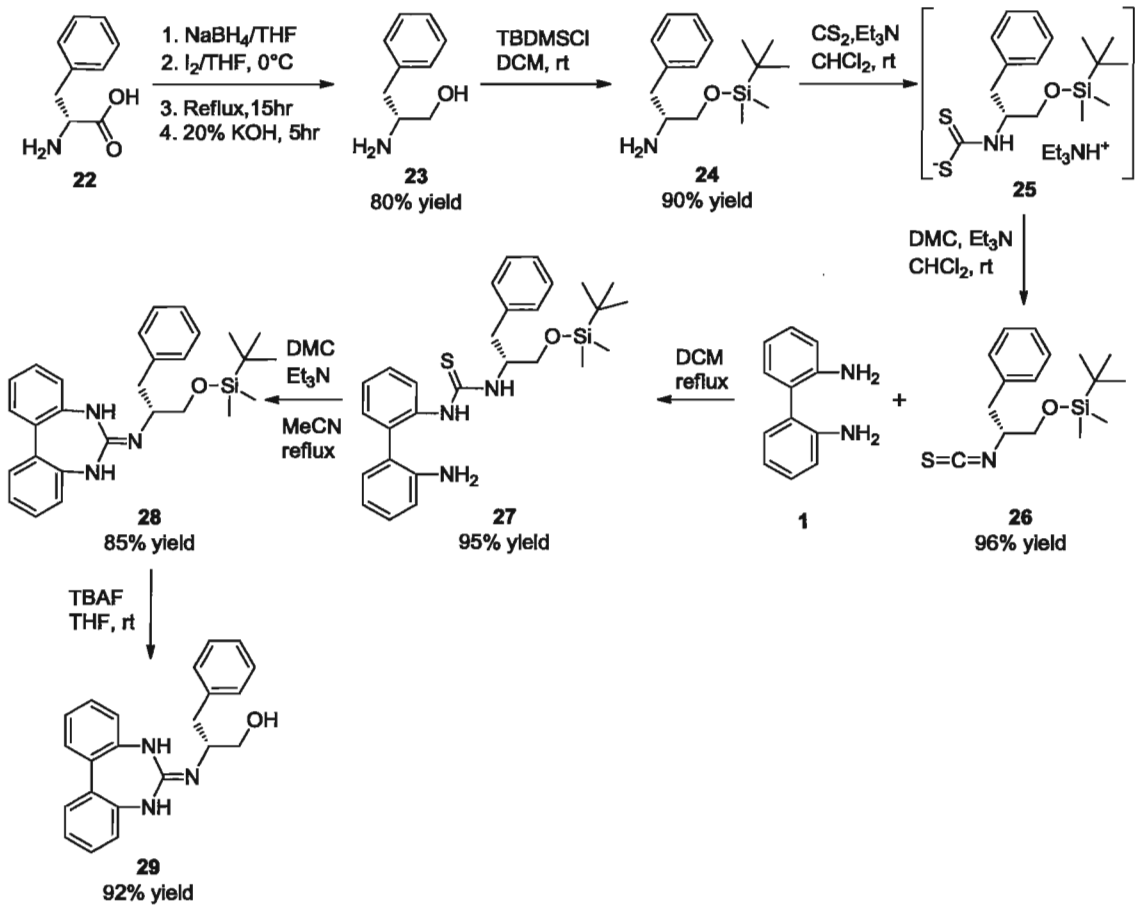
20 21

Scheme II-5: Generation of a guanidine catalyst with axial chirality.

Additionally, following successful implementation of a protocol for guanidine preparation, focus was directed towards the implementation of desired chiral auxiliaries, such as (*R*)-phenylalaninol, through generation of corresponding isothiocynates. Use of this methodology, alongside small modifications, led to the successful generation of our desired guanidine (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol, **29**. In comparison to the previous route, monoacylation of the diamine starting material was not required. Overall, **29** was prepared from (*R*)-phenylalanine and 2,2'-diaminobiphenyl through a seven-step process, shown in Scheme II-6.

The preparation of **29** began with the synthesis of optically active, TBDMS protected (*R*)-phenylalaninol isothiocynate, **26**, which was prepared from its corresponding amino acid, (*R*)-phenylalanine, **22**, via 4 steps. Following a synthetic route by Brenna et al., the carboxylic acid was reduced using $NaBH_4$ and I_2 treatment,[59] forming (*R*)-phenylalaninol, **23,** followed by protection of the free hydroxyl group with TBDMSCl, yielding **24**. Following methodology by Ishikawa et al., **24** was treated with carbon disulfide and triethylamine, forming triethylammonium dithiocarbamate **25,** which underwent a dehydrosulfide reaction using DMC induction, affording (*R*)-*tert*-butyl(2-isothiocyanato-

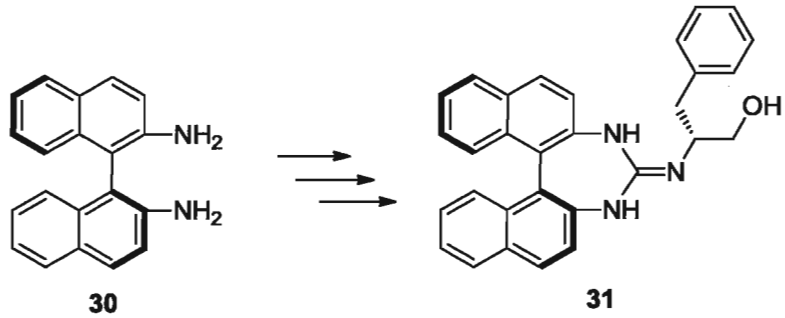
3-phenylpropoxy)dimethylsilane, **26**.[21] (Isobe, 1999) Upon isothiocyanate formation, **26** was treated with unprotected 2,2'-diaminobiphenyl, affording the desired thiourea derivative (R)-1-(2'-amino-[1,1'-biphenyl]-2-yl)-3-(1-((tert-butyldimethylsilyl)oxy)-3-phenylpropan-2-yl)thiourea, **27**. NMR analysis of **27** in $CDCl_3$ and DMSO identified the existence of multiple rotomeric states. The free rotation of the thiourea, alongside its bulky substituents, prevented dithiourea formation with the second available amine, eliminating the need for monoacylation mentioned earlier. This was favourable as it eliminated two steps from the synthetic pathway. Compound **27** was then converted to the corresponding guanidine derivative (*R*)-1-((tert-butyldimethylsilyl)oxy)-*N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3-phenylpropan-2-amine **28,** through DMC-induced cyclization, as described earlier.[22] This derivative affords access to two potential pathways. The first, involves simple deprotection of the hydroxyl group using TBAF, affording (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol, **29**. This *N*-protonated guanidine will be scanned for its potential towards asymmetric catalysis of desired reactions. Additionally, a second pathway which can be explored involves further modification of the guanidine species through *N*-alkylation. This has the potential to provide access to more complex guanidines, such as **8** and **9**, which were unattainable through methods previously discussed.



Scheme II-6: Preparation of (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol.

II-1.3. Synthesis of Guanidines with Axial Chirality

After successfully generating the guanidine catalyst with the (*R*)-phenylalaninol auxiliary, interest shifted towards the application of this catalyst in natural product synthesis, discussed in Section I-3. Alongside this work, interest developed towards incorporation of additional chiral functionality, such as axial chirality, discussed in Section II-2.2. These catalysts were prepared using methods employed in Scheme II-6, catalysts with both (*S*)-(-)-1,1'-Binaphthyl-2,2'-diamine, Scheme II-7, and (*R*)-(+)-1,1'-Binaphthyl-2,2'-diamine, Scheme II-8.



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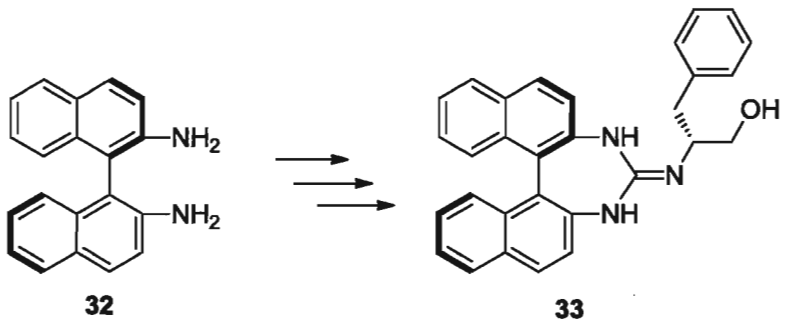
Scheme II-7: Truncated scheme of phenylalaninol guanidine synthesis from (*S*)-(-)-1,1'-Binaphthyl-2,2'-diamine



32 33

Scheme II-8: Truncated scheme of phenylalaninol guanidine synthesis from (*R*)-(+)-1,1'-Binaphthyl-2,2'-diamine

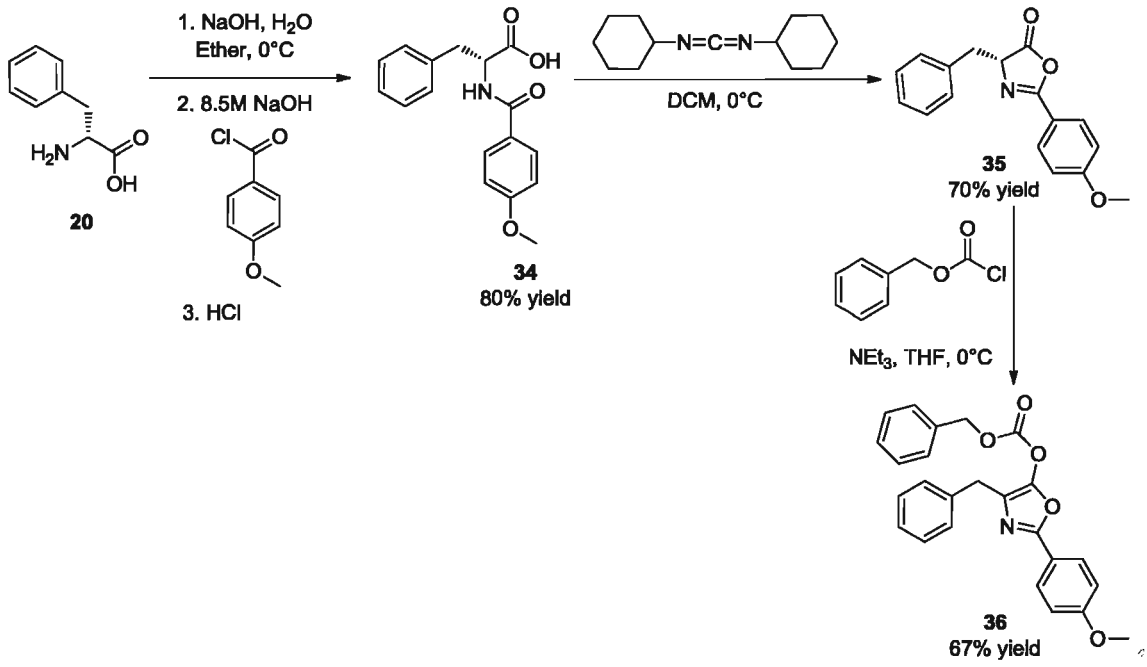
II-2. Enantioselective Catalysis

The synthesized guanidines we prepared were tested for their efficacy for catalysis of desired reactions. Achiral guanidine catalyst N-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl)aniline, **19**, was first used as an reference for accessing the potential of the accessing the desired 7 membered ring guanidine structure.

II-2.1. *O*-Acylated Azalactone Rearrangement.

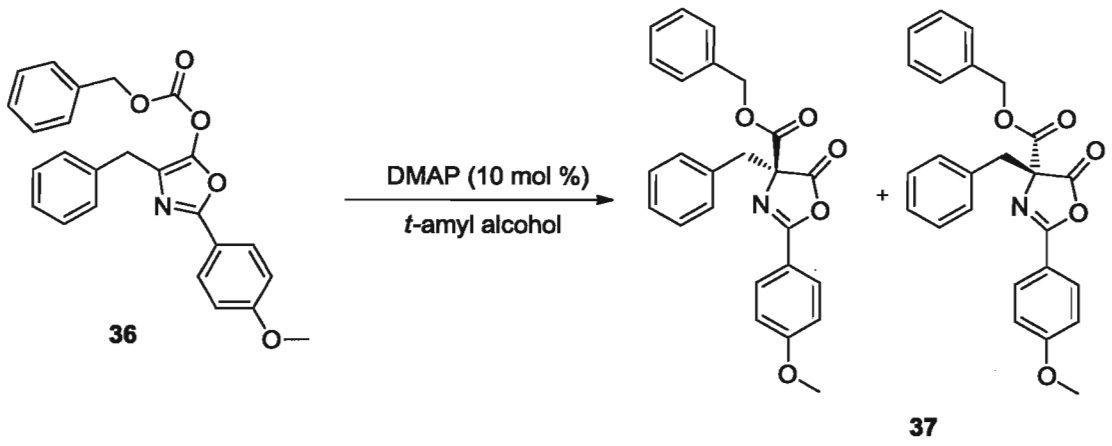
The catalytic potential of **19** for *O*-acylated azalactone rearrangements primarily assessed. This reaction that can be used for entry into synthesis of α-alkylated amino

acids, discussed in Section I-1.2. Specifically, work focused on intermolecular *O*-acyl transfer of benzyl carbonate, **36**, prepared according to the literature, as outline in Scheme II-9.[10] Generation of the final product and all intermediates were confirmed by NMR comparison to literature findings.



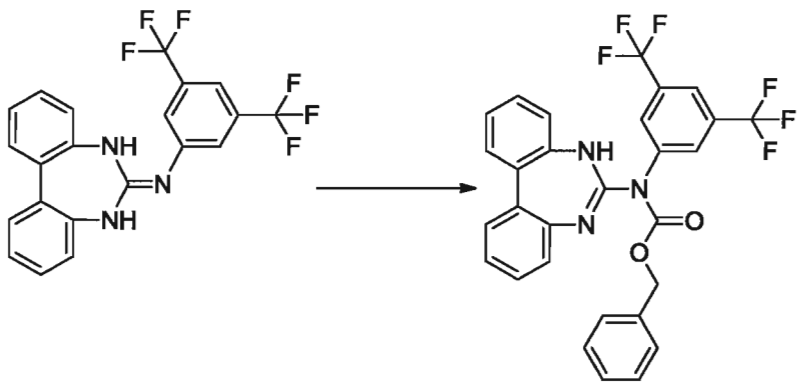
Scheme II-9: Preparation of 4-benzyl-2-(4-methoxyphenyl)oxazol-5-yl from phenylalanine.

The premise of this reaction was that introduction of a catalytic guanidine base, **19**, in the presence of an azalactone, such as **36** would results in formation of an enolized species; followed by successive dissociation of the *O*-acyl group and acylation of the α-carbon. Initially, reaction conditions discovered by Sterglich in 1970 were investigated.[46] Using a catalytic amount of 4-(dimethylamino)pyridine (DMAP) to perform the *O*-acylated azalactone rearrangement, termed the Sterglich rearrangement, illustrated in Scheme II-10, was successful in affording of (S)-benzyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate; confirmed by NMR spectroscopy.



Scheme II-10: *O*-acylated azalactone rearrangement, Sterglich rearrangement.

Upon successful repetition of Sterglich's work, achiral guanidine **19** was used in place of DMAP for catalytic induction. Conversion to product was not observed, however it was observed that catalyst **19** was no longer present and a new product had formed, indicated by thin layer chromatographic analysis. This unexpected reaction was proposed to be a direct result of the guanidine's protons; resulting in an acylated deactivation of the catalyst **19**, shown in Scheme Scheme II-11. It is hypothesized that alkyl protection of these positions, forming a guanidine species such as **8** or **9,** would afford the desired rearrangement product. However, this work was not further investigated due to a lack of *N*-alkylated guanidines.

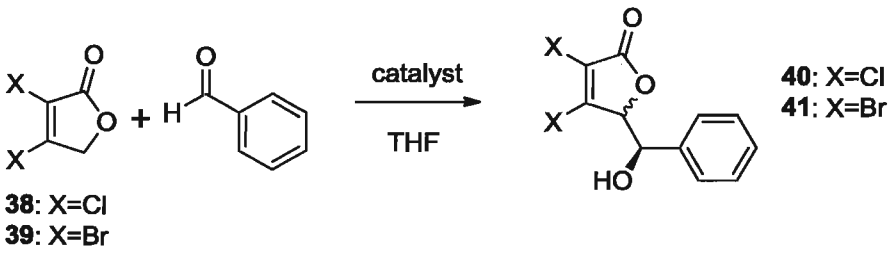


Scheme II-11: Proposed method of guanidine inactivation during *O*-acyl rearrangement.

II-2.2. γ-Substituted Butenolides

Continuing to further explore the potential of catalyst **19**, focused shifted to the development of asymmetric routes for the synthesis of γ-substituented butenolides, a structural motif present in numerous natural product, discussed in Section I-1.1.

To give entry into this field, γ-substitution of 3,4-dichloro-2-(5*H*)-furanone with benzaldehyde was investigated, Scheme II-12. 3,4-dichloro-2-(5*H*)-furanone was readily prepared from a reduction of mucochloric acid.[3] It was found that using 5 mol percent of catalyst **19** in THF was successful in partial product conversion, Table II-1. No diastereotopic or enantiomeric excess were attained with the achiral test guanidine.



Scheme II-12: γ-substitution of 3,4-dichloro-2-(5*H*)-furanone with benzaldehyde.

After confirming successful induction of γ-substitution using the achiral guanidine derivative, **19**, investigation was directed towards utilizing a chiral catalyst for enantioselective induction. For this purpose, the previously discussed guandine with an implemented chiral (R)-phenylalaninol auxiliary, **29**, was utilized. Investigation for asymmetric induction of aforementioned Scheme II-12 using **38**, demonstrated a lower reaction time with a 52 percent enantiomeric excess(ee) and mild diastereotopic ratio (dr), shown in Table II-1, warranting further investigation.

Effort was put forth towards determining the optimal conditions of the catalyst, illustrated in Table II-1 and Table II-2. The reaction was found to give the best yields and enantioselectivies in THF. Additionally, product conversion was determined to increase with time and decrease with low temperatures, however enantioselectivity or diastereoselectivity remained largely unchanged.

Table II-1: Time and Temperature Variance

Entry	Time (hr)	Catalyst (5 mol %)	Temperature (°C)	Solvent	Percent Yield	d.r (anti:syn)	e.e	
							Anti	Syn
1	24	19	rt	THF	14.0	52.0:48.0	0	0
2	24	29	rt	THF	54.2	61.6:38.4	30	52
3	5	29	60	THF	20.4	59.2:40.8	31	45
4	5	29	rt	THF	20.0	61.4:38.6	35	49
5	5	29	0	THF	5.1	58.2:41.8	30	41
6	5	29	-20	THF	<5	59.5:40.5	27	38
7	5	29	-40	THF	<5	57.0:43.0	N.D	N.D

*HPLC results were performed in duplicates

Table II-2: Various Solvents

Entry	Time (hr)	Catalyst (5 mol %)	Solvent	Percent Yield	d.r (anti:syn)	e.e	
						Anti	Syn
1	5	29	THF	20.0	61.4:38.6	35	49
2	5	29	THF/Acetone	18.0	60.8:39.2	35	46
3	5	29	Ether	15.2	54.2:45.8	27	37
4	5	29	TBME	10.1	54.5:45.5	29	37

*HPLC results were performed in duplicates

Further investigation of this catalyst involved scanning specificity towards a variety of derivatives, outlined in Table II-3. Recent reports show incorporation of bulkier halogens on butenolides increase diastereomeric induction.[51] In accordance, catalyst **29** was more selective with dibromo furanone, **39**, in Scheme II-12, opposed to the dichloro species, **38**. These increases are attributed to by greater steric effects created by the larger bromine halogens with the catalyst. Increased interaction results in better asymmetric induction. On the other hand, variation of the aldehyde shows minor differences in enantioselectivity. These results give insight into the alignment of the catalyst during the reaction. Since changes in the furanone backbone result in large ee differences, it suggests they are most likely positioned near the chiral phenylalaninol auxiliary. Mechanistic computational studies are currently ongoing to investigate this reaction. Moreover, since aldehydes possess very little influence on ee, they are most likely aligned above the biphenyl backbone of catalyst **29**, which does not induce enantioselectivity, due to its achiral nature.

Looking further at Table II-3, it is evident that entries 2 and 4 deviate from the normal trends. These entries involve a reaction with dihalofuran-2(5H)-one, **38** and **39** respectively, with 4-chlorobenzaldehyde. Use of the dichloro species exhibits a drastically low ee according to predicted values, while utilizing dibromo furanone affords an exceptionally high ee of 96 percent. Computational studies are being performed in this area to help rationalize the results.

Attempts to increase the enantioselective induction of the (*R*)-phenylalaninol catalyst, **29**, focused towards incorporation of additional chirality. Resulting from the lack of

asymmetric induction by the biphenyl backbone, one such attempt focused on incorporation of axial chirality using [1,1'-binaphthalene]-2,2'-diamine as a backbone for guanidine structure. However, since both (*R*) and (*S*) configuration exist, the synergistic effects between induction of both chiral functionalities were investigated for constructive or destructive selectivity. Preparation of catalysts **31** and **33** was previous discussed in section II-1.3.

Table II-3: Guanidine 29 Catalyzed Reaction with Varying Substrates

Entry	Furanone (X)	Aldehyde, R	% Yield (24 hr)	d.r (anti:syn)	e.e	
					Anti	Syn
1	Cl	C_6H_4	54.2	61.6:38.4	30	52
2	Cl	4-ClC_6H_4	53.0	48.2:51.8	16	20
3	Br	C_6H_4	35.0	52.3:47.7	37	61
4	Br	4-ClC_6H_4	30.5	57.8:42.2	54	96
5	Br	3,5-$(OMe)_2C_6H_4$	15.8	54.6:45.4	35	65
6	Br	4-BrC_6H_4	39.5	52.6:47.4	51	51
7	Br	4-MeC_6H_4	19.1	51.0:49.0	37	58
8	Br	Methyl 4-formylbenzoate	37.1	53.1:46.9	17	55
9	Br	4-$OMeC_6H_4$	14.6	51.0:49.0	39	55
10	Br	4-$CF_3C_6H_4$	40.5	46.0:54.0	22	53

*HPLC results were performed in duplicates

Following synthesis, asymmetric induction of the general reaction outlined in Scheme II-12, was investigated. These results along with a summary of the effects of each guanidine species is given in Table II-4. In the cause of utilizing the dichloro furanone, **38**, it is evident that incorporation of (S)-binaphthyl diamine, yielding catalyst **31**, exhibits mismatched enantiomeric induction with the (D)-phenylalaninol auxillary. However, (R)-binaphthyl diamine exhibits a matched enantiomeric induction, giving a 10 percent increase in enantioseelctivity. However, unlike the previous catalyst, **29**, the utilization of a dibromo furanone, **39**, offered no increases in enantioselectivity, although increases in diastereoselectivity exhibited a 10 percent increase. Future goals are aimed at increasing the enantioselectivity and diastereoselectivity of these γ-substituted butenolide reactions, discussed in more depth below.

Table II-4: Various Catalysts

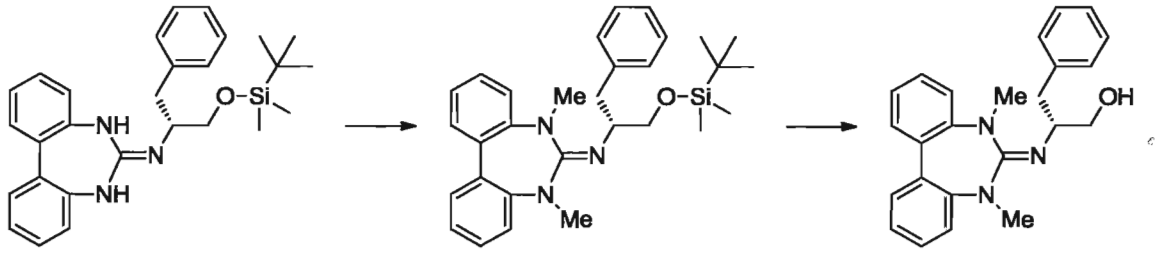
Furanone (X)	Catalyst (5 mol %)	Percent Yield	d.r(anti:syn)	e.e	
				Anti	Syn
Cl	19	20.0	52.0:48.0	0	0
Cl	29	54.2	61.4:38.6	35	49
Br	29	35.0	52.3:47.7	37	61
Cl	31	33.1	59.5:40.5	12	16
Cl	33	31.1	60.1:39.9	42	62
Br	33	26.1	50.3:49.7	44	64

*HPLC results were performed in duplicates

II-3. Future Work

II-3.1. Development of *N*-alkylated Guanidines

Future work in this field is focused on preparation of *N*-methylated guanidine **8** and *N*-benzylated guanidine **13**, allowing for reassessment of *O*-acyl azalactone rearrangements along with providing catalysts offering new potential asymmetrically inductive properties to enantioselective γ-substituted butenolides. To date, methylation utilizing butyl lithium as a deprotonating agent followed by successive treatment with methyl iodide have been unsuccessful. Another potential method for *N*-methylation involves previously employed methods utilizing sodium hydride and methyl iodide, which are not as harsh.[17] *N*-benzylation of the guanidines can be attempted through methods discussed earlier by Kostyanovsky[30], involving alkyl halides, KOH and DMSO.



Scheme II-13: Potential Scheme for *N*-benzylation of phenylalaninol guanidines.

II-3.2. Modification of Axial Chiral Backbone

Furthermore, work will be directed towards implementation of additional steering groups on the binaphthyl backbone, illustrated in Figure II-2 as R_1. Expanding the steric bulkiness of the binaphthyl backbone has the potential to generate additional asymmetrically inductive effects on the reaction, by increasing the effects of the axial chirality.

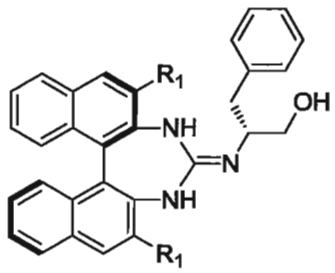


Figure II-2: Guanidine catalyst with potential location for additional R_1 attachment groups.

III. Experimental

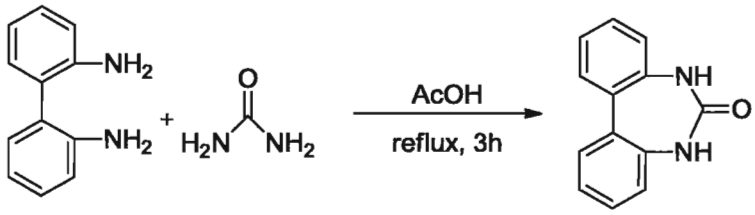
III-1. General Methods

All reactions were performed under N_2 in oven dried glassware. Flash chromatography was performed using distilled solvents from Sigma-Aldrich and Caledon. Chromatographic purifications were performed using Silicycle Siliaflash P60 40-63 μm (230-400 mesh) silica gel with the indicated solvents as eluents. TLC analysis was performed using EMD TLC Silica gel 60 F_{254} aluminium sheets and visualized using UV light, iodine and potassium permanganate and ninhydrin stains. NMR analysis was performed using the Bruker 300 Ultrasheild 300 MHz NMR and the Bruker 600 Plus Ultrasheild 600 MHz NMR. Optical rotations were determined using the Autopol III automatic polarimeter. Mass spectroscopy analysis was performed using the Kratos Analytical/ MSI Concept 1S.

III-2. General Procedures

III-2.1. Approaches to Guanidines Utilizing Iminium Chloride and Amine Coupling

General procedure for synthesis of 5H-dibenzo[d,f][1,3]diazepin-6(7H)-one (3):



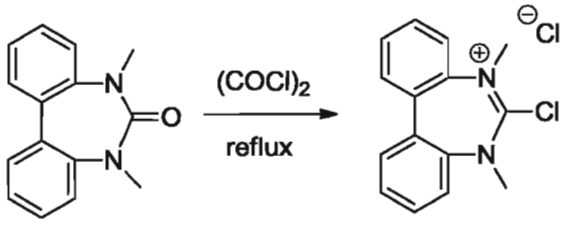
Following the reported procedure[30], AcOH was added to a mixture of 2,2'-diaminobiphenyl (1 equiv.) and urea (2 equiv.) and the solution was refluxed for 3 hours. The solution was diluted with isoproponal and cooled in an ice bath. The residue was filtered, washed with isoproponal and dried in vacuo, yielding biphenyl urea (70% yield). Recrystallization was performed from BuOH, resulting in an off-white powder. ^{1}H NMR (DMSO, 300 MHz) δ 8.793 (s, 2H, N-H), 7.469-7.443 (m, 2H, Ar-H), 7.305-7.302 (m, 2H, Ar-H), 7.184-7.082 (m, 4H, Ar-H).

General procedure for synthesis of 5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-one (4):

Following the procedure by Isobe et al,[17] NaH (55% in mineral oil, 2.2 equiv.) washed with dry hexanes under N_2, followed by suspension in DMF. Biphenyl urea (1 equiv.), was dissolve dissolved in DMF and added dropwise to the stirred suspension of NaH and was let stir at room temperature for 1 hour. Iodomethane (2.2 equiv.) was then added

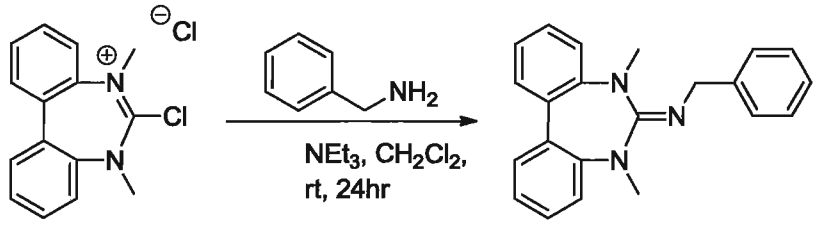
dropwise to the mixture and let stir at room temperature overnight. The reaction was poured into 5% HCl and extracted with dichloromethane (2 x 100ml). The organic layer was washed with water and dried with $MgSO_4$. Purification of the residue by column chromatography and recrystallization in MeOH afforded the product as colourless prisms (95% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.519 – 7.211 (m, 8H, Ar-H), 3.228 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 166.02, 144.93, 132.90, 128.67, 128.46, 124.83, 119.75, 36.33.

General procedure for synthesis of 6-chloro-5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-7-ium chloride (5):



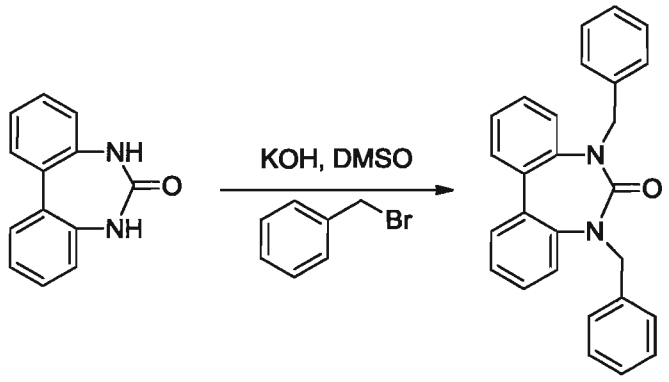
5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-one (1 equiv.) was added to a reflux apparatus and put under and N_2 atmosphere. Oxalyl chloride (5 equiv.) was added, followed by a catalytic amount of DMF (2 drops). The reaction was heated to 60°C and let stir overnight. Excess oxalyl chloride was removed under reduce pressure, yielding the product (60% conversion) as a yellow solid. No further purification was performed. Product conversion was determined by NMR. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.922 (Chloroiminium: N- CH_3), 3.192 (Urea: N- CH_3).

General procedure for synthesis of *N*-(5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-1-phenylmethanamine (7):



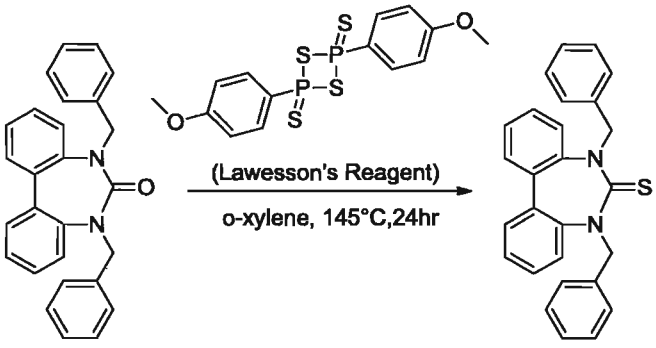
According to the reported procedure[43], to a solution of benzyl amine (1 equiv.) in DCM (0.18M) was added NEt_3 (2 equiv.). This mixture was added dropwise to a stirred solution of 6-chloro-5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-7-ium. The mixture was stirred at room temperature for 6 hours, poured into 5% HCl, and extracted with DCM. The solvent was evaporated and the residue was dissolved in water, and washed with toluene (2 x 50ml). The aqueous solution was made basic with 5% NaOH, extracted with water and dried over Na_2SO_4. Solvent evaporation yielded the pure guanidine (76% yield) as a white solid. Column chromatography could also be used for purification. White crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.587 – 7.203 (m, 13H, Ar-H), 4.829 (s, 2H, N-H), 3.356 (s, 3H, N- CH_3), 3.166 (s, 3H, N- CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 160.22, 145.66, 145.51, 143.00, 137.91, 136.62, 133.89, 129.12, 128.71, 128.53, 128.47, 128.40, 128.31, 126.45, 126.25, 125.89, 125.39, 124.54, 121.85, 52.74, 40.71, 38.50. m/z = 327.

General procedure for synthesis of 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-one (10):



Biphenyl urea (1 equiv) and crushed KOH (4 equiv) were dissolved in DMSO (1.25 M), followed by the addition of benzyl bromide (4 equiv.) and was let stir overnight. Water was added, forming an amorphous precipitate which was filtered off and dried under vacuum. To remove any residual DMSO, the compound was recrystallized using EtOH (Yield 65%). Off-white crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.504-7.499 (m, 2H, Ar-H), 7.479-7.214 (m, 7H, Ar-H), 7.105-7.093 (m, 6H, Ar-H), 6.961-6.931 (m, 4H, Ar-H), 5.213-5.162 (d, 2H, CH_2), 4.702-4.652 (d, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 164.93, 143.43, 137.64, 134.09, 128.41, 128.19, 127.24, 126.79, 125.27, 121.23, 52.03.

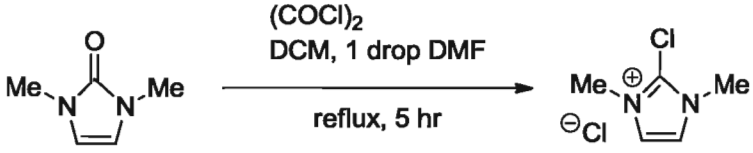
General procedure for synthesis of 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepine-6(7H)-thione (11):



Benzyl urea (1 equiv.) and Lawesson's reagent (2 equiv.) were dissolved in *o*-xylene (0.24M in respect to benzyl urea). The mixture was heated to 145°C and let stir for 24 hours. The reaction was quenched using a 3.75:1 biphasic solution of methanol and 5% aqueous HCl and was let stir at room temperature overnight. The organic layer was isolated and the aqueous phase was extracted with toluene. The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (SiO_2, hexane:ethyl acetate, 50:1) affording the product. Recrystallization from ether-hexanes gave white crystals (91% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.415-7.270 (m, 8H, Ar-H), 7.061-7.7.038 (m, 6H, Ar-H), 6.861-6.830 (m, 4H, Ar-H), 5.840-5.789 (d, 2H, CH_2), 4.896-4.845 (d, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 199.48, 145.58, 136.93, 135.53, 128.41, 128.01, 127.86, 127.58, 126.81, 126.45, 122.06, 57.42.

III-2.2. Approaches to Guanidines Utilizing DMC-Induced Thiourea Cyzlization

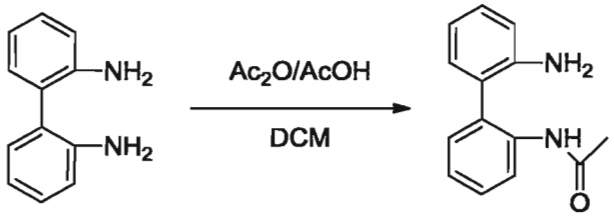
General procedure for synthesis of 2-chloro-1,3-dimethyl-1H-imidazol-3-ium chloride:



1,3-dimethyl-2-imidazolidinone (1 equiv.) under an N_2 atmosphere was dissolved in dry DCM. Oxalyl chloride (1.5 equiv.) was added, followed by a catalytic amount of DMF and the reaction was set to reflux for 5 hours. The solvent was removed under reduced pressure and the resulting solid was washed with ether (3 washes) under an N_2 atmosphere, yielding 85% product as yellow crystals.

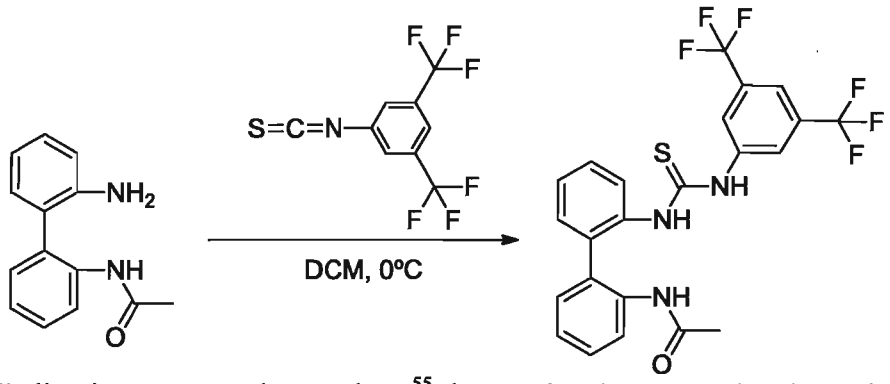
III-2.2.1. Biphenyldiamine Backbone with a Trifluoro Auxiliary

General procedure for the generation of *N*-(2'-amino-[1,1'-biphenyl]-2-yl)acetamide (14):



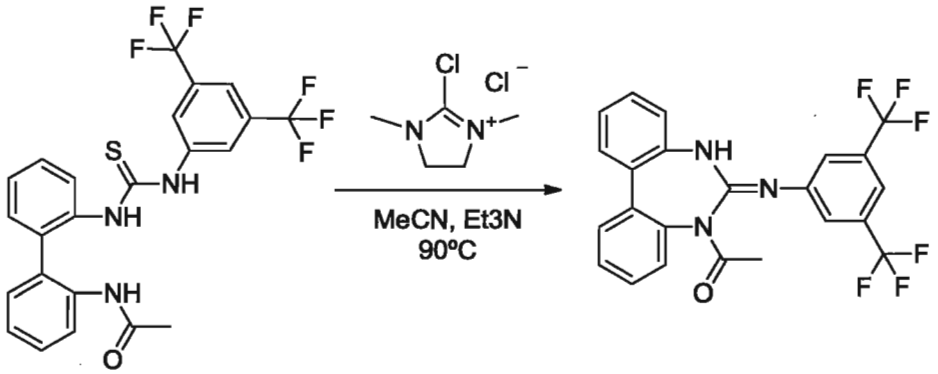
Following a slight modification of the reported procedure,[1] [1,1'-biphenyl]-2,2'-diamine (1 equiv) was dissolved in dry CH_2Cl_2 (0.1M), followed by addition of AcOH (10 eq.) under N_2. After 10 minutes, acetic anhydride (0.9 equiv) was added drop wise at 0 °C under N_2. The solution was let stirred overnight at room temperature and then neutralized to a pH≈7 by addition of 2*N* NaOH. The reaction mixture was extracted with CH_2Cl_2 (3× 25 mL), the organic layers were combined, washed with saturated brine (25 mL) and dried over $MgSO_4$. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography to give 78% yield. Beige crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.226-8.199 (d, 1H, Ar-H), 7.507 (s, 1H, N-H), 7.425-6.806 (m, 7H, Ar-H), 3.623 (s, 2H, NH_2), 2.011 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 168.56, 143.56, 135.68, 131.16, 130.74, 129.44, 129.28, 128.71, 124.70, 123.52, 122.25, 119.29, 115.70, 24.67.

General procedure for synthesis of the corresponding biphenyl diamine thiourea, *N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)acetamide (16):



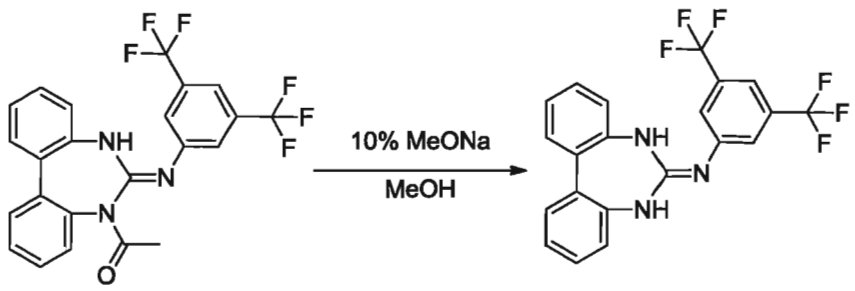
Following a reported procedure,[55] the previously prepared *N*-(2'-amino-[1,1'-biphenyl]-2-yl)acetamide (1 equiv) was dissolved in dry CH_2Cl_2 (0.06M) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.2 equiv) was added dropwise at 0°C under N_2. The solution was stirred overnight at room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (Ethyl Acetate:Hexanes 1:10) to give 95% yield. Yellow tinged solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.802-7.319 (11H, Ar-H) 1.884 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 179.99, 168.68, 141.96, 136.44, 135.85, 135.43, 131.08, 130.39, 130.26, 129.83, 129.04, 128.78, 128.42, 127.36, 125.44, 125.13, 124.39, 121.83, 117.37, 23.64.

General procedure for the synthesis of 1-(6-((3,5-bis(trifluoromethyl)phenyl)imino)-6,7-dihydro-5H-dibenzo[d,f][1,3]diazepin-5-yl)ethanone (18):



Cyclization to the subsequent guanidinium species was achieved by dissolving the prepared N-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)acetamide (1 equiv) and DMC (2-chloro-1,3-dimethylimidazolinium chloride) (1.2 equiv.) in MeCN (0.0151M), adding Et3N (3 equiv.) and refluxing the mixture. Work up involved addition of the reaction mixture to water and extraction by CH_2Cl_2 (2× 30 mL). Purification by column chromatography (SiO_2) (Ethyl Acetate:Hexane 1:2) to give 79% yield of guanidinium species. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.318 (s, 1H, N-H), 8.182-7.240 (11H, Ar-H), 1.893 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 144.22, 141.54, 140.93, 138.65, 136.33, 131.69, 131.24, 129.95, 129.77, 129.52, 129.37, 129.03, 128.82, 127.42, 126.76, 125.01, 124.23, 121.40, 117.86, 115.69, 22.65.

General procedure for the synthesis of *N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl)aniline (19):

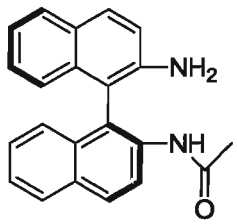


The acyl protecting group of previously prepared 1-(6-((3,5-bis(trifluoromethyl)phenyl)imino)-6,7-dihydro-5H-dibenzo[d,f][1,3]diazepin-5-yl)ethanone (1 equiv.) was removed by treatment with 10% MeONa in MeOH for 1.5hours at room temperature. The resulting solution was poured into water and extracted with CH_2Cl_2 (2× 30 mL). The obtained residue was purified by column chromatography (SiO_2) to give 90% yield of product. White powder after crystallization. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.540-7.004 (8H, Ar-H), 6.656, (s, 1H, N-H), 5.756 (s, 1H, N-H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 158.985, 149.467, 133.645, 133.206, 132.769, 132.330, 129.500, 129.008, 125.417, 125.074, 123.680, 121.454, 116.421. m/z = 327.

III-2.2.2. Binaphthyldiamine Backbone with a Trifluoro Auxiliary

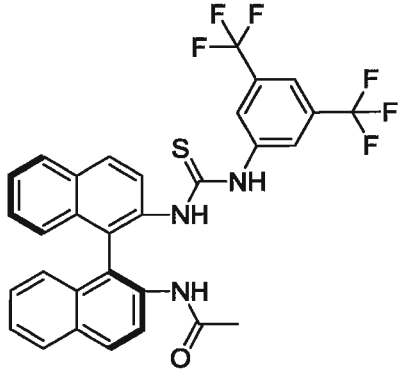
The general procedures outlined above were also followed for the synthesis of guandines containing binaphthyl backbones.

(*S*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl) acetamide



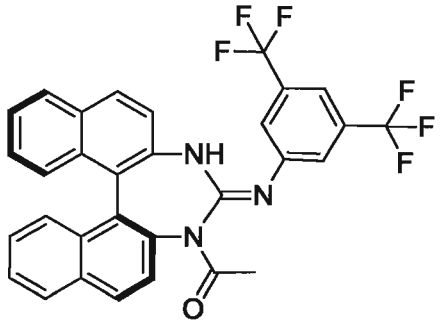
Clear colorless oil. ^{1}H NMR ($CDCl_3$, 300MHz) δ 8.650 (d, 1H; RNHOCH3), 8.001 (d, 1H; Ar-H), 7.872 (multiplet, 3H; Ar-H), 7.415 (t, 1H; Ar-H), 7.181 (multiplet, 5H; Ar-H), 6.919 (d, 1H, Ar-H), 3.682 (s, 2H; NH_2), 1.873 (s, 1H; OCH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 168.73, 142.78, 135.11, 133.63, 132.41, 131.31, 130.38, 129.24, 128.25, 128.24, 127.33, 126.84, 125.46, 125.14, 123.65, 122.75, 120.94, 120.54, 118.09, 110.37, 24.73. m/z = 326.

(*S*)-*N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-1,1'-binaphthyl-2-yl)acetamide



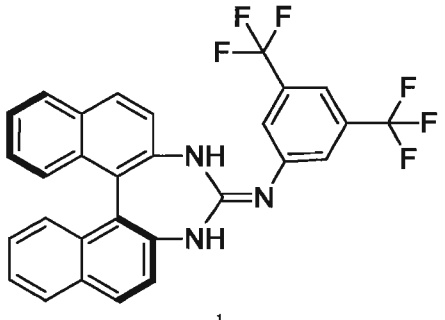
Yellow tinged solid. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.984 (multiplet, 8H; Ar-H), 7.625 (s, 1H; Ar-H), 7.475 (multiplet, 2H; Ar-H), 7.246 (multiplet, 3H; Ar-H), 7.036 (d, 2H; Ar-H) 1.747 (s, 1H; OCH_3) ^{13}CNMR ($CDCl_3$, 300 MHz) δ 181.15, 170.89, 141.02, 135.68, 134.35, 132.94, 132.74, 132.49, 131.98, 131.85, 131.40, 130.97, 130.53, 128.85, 128.13, 126.91, 126.54, 126.42, 126.36, 125.92, 125.54, 125.51, 125.26, 125.00, 123.96, 123.13, 121.40, 117.16, 117.12, 78.05, 21.74. m/z = 597.

(*S*)-1-(4-(3,5-bis(trifluoromethyl)phenylimino)-4,5-dihydro-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-3-yl)ethanone



Yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.723 (s, 1H; NH), 8.241 (s, 1H; Ar-H), 8.031 (multiplet, 3H; Ar-H), 7.935 (d, 1H;Ar-H), 7.787 (d, 1H; Ar-H), 7.627 (d, 1H;Ar-H) , 7.494 (multiplet, 4H; Ar-H), 7.335 (multiplet, 3H; Ar-H) 2.060 (s, 1H, OCH_3). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 170.27, 145.06, 143.78, 140.64, 138.95, 133.54, 132.43, 131.83, 131.61, 131.39, 131.24, 131.17, 130.61, 130.52, 129.95, 128.68, 128.46, 128.40, 127.11, 126.99, 126.95, 126.13, 125.99, 125.91, 124.85, 124.10, 123.63, 122.36, 122.29, 120.49, 117.92, 115.86, 21.95. m/z = 563.

(*S*)-*N*-(3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)-3,5-bis (trifluoromethyl)aniline (21)

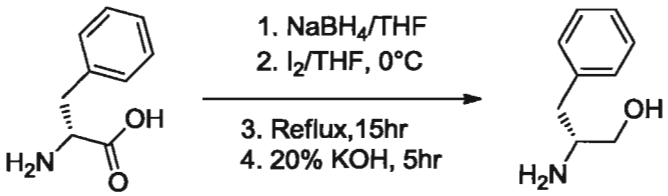


Off-white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.933 (d, 2H; Ar-H), 7.902 (d, 2H; Ar-H), 7.609 (s, 1H; Ar-H), 7.426 (s, 4H; Ar-H), 7.358 (d, 1H; Ar-H), 7.206 (multiplet, 4H; Ar-

H), 6.982 (s, 2H; Ar-H), 5.948 (s, 1H, Ar-H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 160.17, 149.41, 140.22, 138.49, 133.38, 133.16, 132.94, 132.72, 132.38, 131.43, 131.32, 130.09, 129.92, 128.20, 127.31, 127.13, 126.54, 126.42, 125.98, 125.38, 125.12, 124.89, 124.17, 123.74, 123.55, 122.36, 121.63, 120.56, 120.23, 116.60. m/z = 521.

III-2.2.3. Biphenyldiamine Backbone with a Phenylalaninol Auxiliary

General procedure for synthesis of (*R*)-2-amino-3-phenylpropan-1-ol (23):

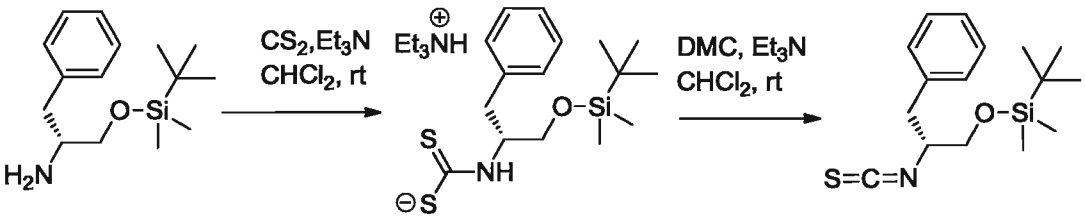


Following a procedure reported by Brenna et al.,[59] phenylalanine (1equiv.) was slowly added to a stirred suspension of $NaBH_4$ in THF (2.5 equiv.) and subsequently cooled to 0°C. A solution of I_2 (1 equiv.) in THF was prepared and added drop wise, maintaining a temperature below 20°C. Once evolution of H_2 had ceased after addition of I_2 was complete, the reaction was refluxed overnight. After cooling the reaction to room temperature, MeOH was added to exhaust excess $NaBH_4$ and let stir for 45 minutes. The solvent was evaporated under N_2 and the residual white paste was dissolved in 20% (w/w) KOH and stirred for 4 hours. The mixture was extracted with dichloromethane (3 x 50mL), dried with $NaSO_4$ and solvent was removed by rotary evaporation, yielding a white solid. (80% yield).

General procedure for synthesis of (*R*)-1-((tert-butyldimethylsilyl)oxy)-3-phenylpropan-2-amine (24):

Following a procedure by Ishikawa et al.,[18] TBDMSCl (1 equiv) was dissolved in dry dichloromethane under an N_2 atmosphere. The solution was added dropwise to a solution of (S)-phenylalaninol (1equiv.), 4-(dimethylamino) pyridine (0.2 equiv.), Et_3N (2 equiv.) in dichloromethane (0.66M with respect to phenylalaninol). The reaction was stirred at room temperature for 24 hours and poured into water; followed by extraction with DCM. The obtained residue was purified through column chromatography (SiO_2, 10:1 hexanes:ethyl acetate) yeilding 90% product.

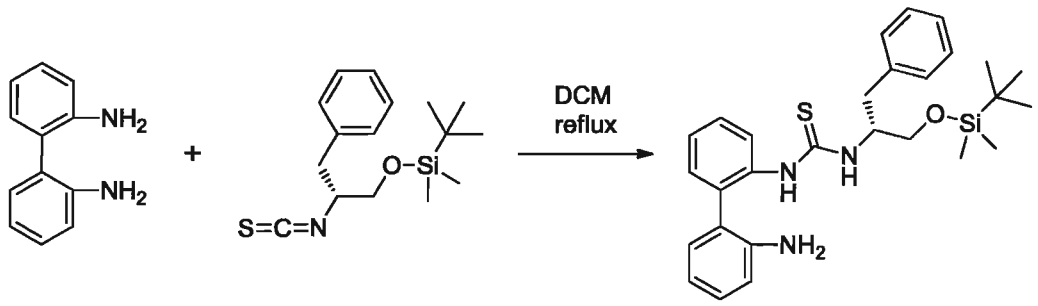
General procedure for synthesis of (R)-tert-butyl(2-isothiocyanato-3-phenylpropoxy) dimethylsilane (26):



The TBDMS protected phenylalaninol (1 equiv.) was dissolved in DCM (giving 0.167M solution) under an N_2 atmosphere, followed by addition of Et_3N. After 5 minutes CS_2 was added dropwise and the reaction was let stir for 2 hours at room temperature. This was followed by addition of a 1.2 M solution of DMC (1.2 equiv.) in DCM. The reaction was

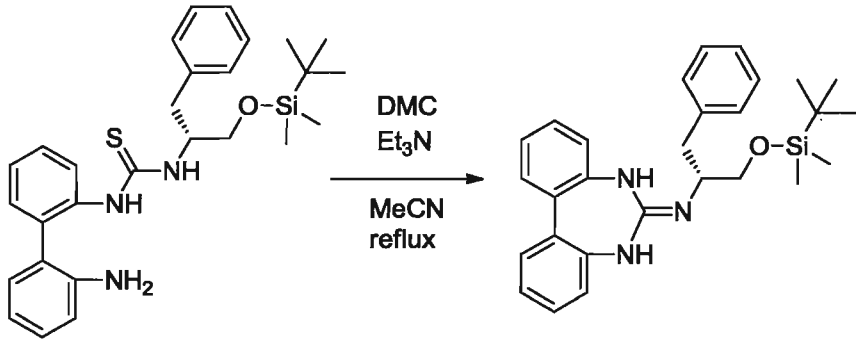
let stir at room temperature for 24 hours and evaporated. Purification by column chromatography gave the product (96% yield) as a colourless oil.

General procedure for synthesis of (*R*)-1-(2'-amino-[1,1'-biphenyl]-2-yl)-3-(1-((tert-butyldimethylsilyl)oxy)-3-phenylpropan-2-yl)thiourea (27):



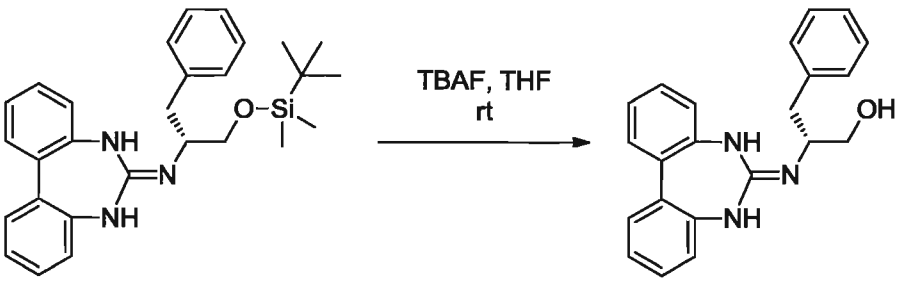
2,2'-diaminobiphenyl (1 equiv.) and the TDBMS protected phenylalaninol thioisocyanate (1 equiv.) were dissolved in DCM and refluxed for 24 hours. Following evaporation, the residue was purified through column chromatography (SiO_2, 5:1 hexanes:ethyl acetate). The product was obtained in 95% yield after recovery of starting materials, which were resubjected to the reaction conditions. Clear and colourless oil. ^{1}H NMR (DMSO, 300 MHz) δ 8.877-8.812 (d, 1H; N-H), 7.432-6.606 (m, 13H; Ar-H), 4.716-4.647 (d, 2H, NH_2), 4.559 (m, 1H, CH), 3.507-3.456 (m, 2H, CH_2), 2.868-2.770 (m, 2H, CH_2), 0.861 (s, 9H, $3CH_3$), 0.020 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 300 MHz) Rotamers Present. δ 179.70, 179.44, 142.99, 149.89, 138.12, 135.34, 135.03, 132.51, 130.57, 129.50, 129.45, 129.07, 128.48, 128.41, 127.52, 127.31, 126.48, 126.37, 125.99, 125.10, 124.82, 119.75, 116.80, 116.67, 61.56, 57.34, 57.16, 36.40, 36.27, 25.86, 25.80, 18.13, 18.06, -5.53, -5.69.

General procedure for synthesis of (*R*)-1-((tert-butyldimethylsilyl)oxy)-*N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3-phenylpropan-2-amine (28):



Thiourea (1 equiv.) and DMC (1.2 equiv.) were dissolved in MeCN under an N_2 atmosphere. Et_3N (3 equiv.) was added and the mixture was set to reflux for 13 hours. The reaction was then poured into water and extracted with DCM. The residue was purified by column chromatography (SiO_2, 5:1 Hexanes:Ethyl acetate) affording the product (85% yield) as a colourless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.433-7.132 (m, 13H; Ar-H), 4.015 (m, 1H; CH), 3.761-3.703 (m, 1H; CH_2), 3.618-3.569 (m, 1H, CH_2), 2.961-2.941 (dd, 1H, CH_2), 2.864-2.858 (dd, 1H, CH_2), 0.887 (s, 9H, $3CH_3$), 0.044-0.036 (d, 6H, $2CH_3$).

General procedure for synthesis of (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol (29):

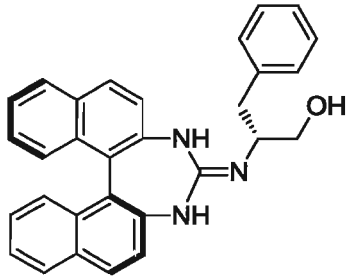


The cyclized guanidine was dissolved in THF under N_2(g), followed the the addition of 1M TBAF in THF. The mixture was let stir for 2 hours at room temperature and then poured into aqueous 5% NaOH solution and extracted with DCM. The residue was purified through coloumn chromatography (SiO_2, 1:1 Hexanes:Ethyl acetate) to afford the product (92% yield) a colourless oil. Washing with hexanes crashed the product out as a white precipitate. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3776.937 (m, 13H; Ar-H), 3.958-3.889 (m, 1H; CH), 3.675-3.633 (dd, 1H; CH_2), 3.515-3.480 (m, 1H, CH_2), 2.863-2.792 (dd, 1H, CH_2), 2.680-2.611 (dd, 1H, CH_2), 0.887 (s, 9H, $3CH_3$), 0.044-0.036 (d, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 160.57, 141.98, 137.20, 131.29, 129.63, 129.47, 129.18, 128.99, 128.79, 128.76, 128.52, 126.87, 125.55, 66.74, 58.01, 37.31. m/z = 343.

III-2.2.4. Binaphthyldiamine Backbone with a Phenylalaninol Auxiliary

The general procedures outlined above, were also employed for the synthesis of the (*R*)-(+) and (*S*)-(-) binaphthyl compounds outlined in place of the biphenyl backbone.

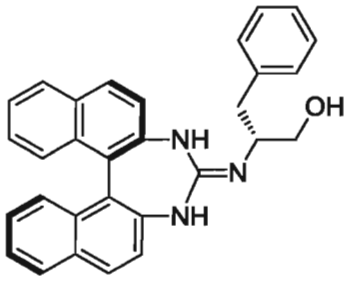
(*S*)-(-)-binaphthyl phenylalaninol guanidine catalyst 31.



White powder after crystallization.^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.9127.845 (m, 5H; Ar-H), 7.422-7.063 (m, 12 Ar-H), 3.804-3.774 (m, 1H; CH_2), 3.734-3.704 (m, 1H; CH), 3.011-2.932 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 160.58, 141.98, 137.20,

131.30, 129.63, 129.56, 129.47, 129.18, 128.99, 128.79, 128.76, 128.87, 125.55, 125.19, 66.74, 58.01, 37.31. m/z = 443

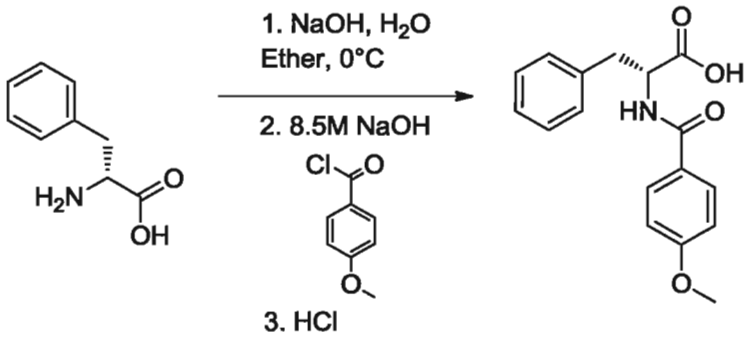
(*R*)-(-)-binaphthyl phenylalaninol guanidine catalyst 33.



White powder after crystallization. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.9127.845 (m, 5H; Ar-H), 7.422-7.063 (m, 12 Ar-H), 3.804-3.774 (m, 1H; CH_2), 3.734-3.704 (m, 1H; CH), 3.011-2.932 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 163.10, 142.95, 137.10, 132.28, 131.44, 129.30, 129.16, 128.98, 128.61, 128.00, 127.01, 126.69, 126.02, 124.96. m/z = 443

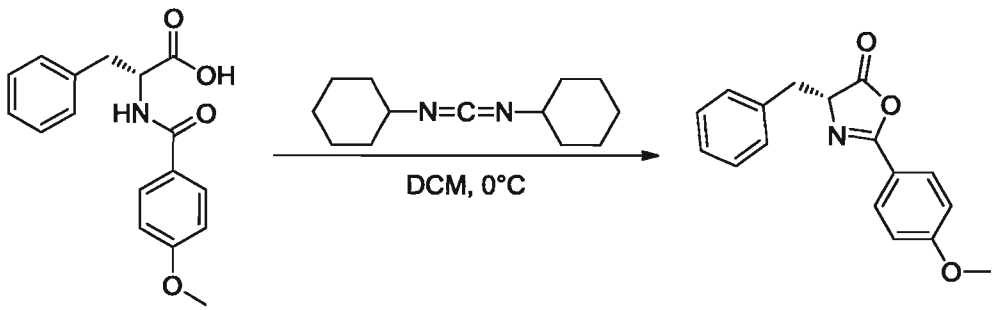
III-3. *O*-acyl Azalactone Rearrangement and Reactant Preparation

General procedure for synthesis of (*R*)-2-(4-methoxybenzamido)-3-phenylpropanoic acid (34):



Following a protocol employed by Fu et al.,[10] (D)-phenylalanine (1 equiv.) was dissolved in a 3.4M solution of NaOH (1.1 equiv.). Subsequently, ether (5 x water volume) was added and the reaction was cooled to 0°C. *p*-Anisoyl chloride and an 8.5M solution of NaOH (1.1 equiv.) were alternately added over 1.5 hours and the reaction was let warm to room temperature overnight. Ether was then removed by rotoevaporation and concentrated HCl was added to the residue resulting in precipitation of the product. Recrystallization was achieved with hot acetone yielding the product as white crystals. (80% yield). Comparison of NMR data to literature confirmed product. [10]

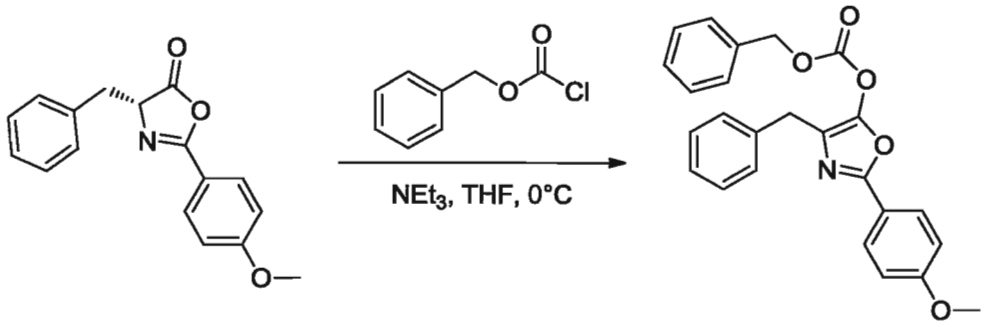
General procedure for synthesis of (*R*)-4-benzyl-2-(4-methoxyphenyl)oxazol-5(4H)-one (35):



Following a protocol employed by Fu et al.,[10] a solution of *N,N*-dicyclohexylcarbodiimide (DCC) (1 equiv.) in DCM (0.83M) was added dropwise to a 0°C mixture of *N*-anisoyl-(D)-phenylalanine (1 equiv.) in DCM (0.19M). The resulting mixture was let stir overnight, allowing for warming to room temperature. The resulting precipitate was removed by filtration and the solvent of the resulting solution was removed by rotoevaporation affording a white solid. Recrystallization was achieved using a 4:1 pentane:DCM in a freezer. Crystals were washed with cold pentane and dried in

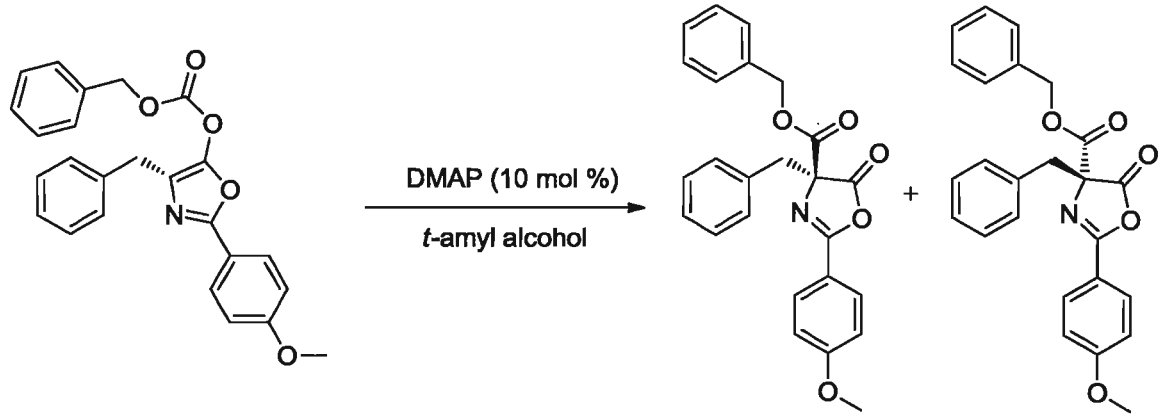
vacuum, affording the product (70% yield). Comparison of NMR data to literature confirmed product.[10]

General procedure for synthesis of benzyl (4-benzyl-2-(4-methoxyphenyl)oxazol-5-yl) carbonate (36):



Following a protocol employed by Fu et al.,[10] a solution of 2-(4-methoxyphenyl)-4-benzyloxazalone (1 equiv.) in THF (0.05M) was cooled to 0°C and NEt_3 was then added (1.1 equiv.). Followed was the addition of benzyl chloroformate (1.05 equiv.), forming a white precipitate and the mixture was stirred overnight. THF was evaporated and the resulting residue was dissolved with ether and partitioned with 1M HCl (1:1). The organic layer was separated, washed with 1M HCl, followed by brine, and dried over $MgSO_4$. Evaporation of solvent gave a residue which was purified by flash chromatography (SiO_2, ether:pentane, 1:9 followed by 1:4) affording the product as a yellow oil (67% yield). Comparison of NMR data to literature confirmed product.[10]

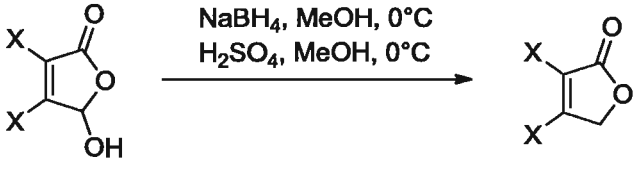
General procedure for synthesis of (*S*)-benzyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (37):



According to literature,[10] benzyl (4-benzyl-2-(4-methoxyphenyl)oxazol-5-yl) carbonate (1 equiv.) was dissolved with *t*-amyl alcohol in an N_2 atmosphere, in a vial equipped with a stir bar, affording a 0.25M solution. Additionally, the catalyst (DMAP or guanidine catalyst) (10 mol %) was dissolved in a separate vial with *t*-amyl alcohol. Both solutions were cooled in an ice bath, followed by cannulation of catalyst solution to the azalactone solution. Reaction completion was determined by NMR as compounds are sensitive to Si_2O. Comparison of NMR data to literature confirmed product.[10]

III-4. Vinylogous Aldol Reaction

A general procedure for synthesis of 3,4-dichlorofuran-2(5H)-one (38, 39):



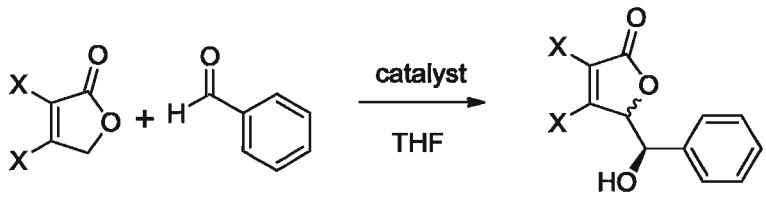
Following a protocol employed by Bellina et al.,[3] Mucochloric acid (1 equiv.) was dissolved MeOH (giving a 0.66M solution) and cooled to 0°C. Sodium borohydride (1.5

equiv.) was added portionwise and then stirred for 30 minutes. A 2M solution of concentrated sulfuric acid (1 equiv.) in methanol, cooled to 0°C, was then added to the reaction. The mixture was kept cold for 10 minutes and then concentrated under reduce pressure. The residue was washed with brine (4 x MeOH volume) and extracted with diethyl ether (5 x (2 x MeOH volume)). The extract was dried under reduced pressure and recrystalized from 1:1 pentane:diethyl ether giving pure product as a colourless solid, in 88% yield. Spectral properties are in satisfactory agreement with reported values.[3]

III-4.1. Generation of Vinylogous Aldol Adducts

General procedure for synthesis of 3,4-dihalo-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one:

The following protocol was employed for the generation of the all vinylogous aldol adducts listed in Table II-3.



A solution of 3,4-dihalo-2-(5*H*)-furanone (1 equiv.) and benzaldehyde were prepared in THF (0.5mL). To this solution, catalyst (5 mol %) was added and the reaction was let stir for 5 hours to 24 hours. The reaction was quenched using saturated aqueous NH_4Cl, extracted with ethyl acetate and dried over Na_2SO_4. The solvent was evaporated, giving a residue that was purified by column chromatography (SiO_2, hexanes:ethyl acetate, 5:1) affording the product in various yields dependent on conditions.

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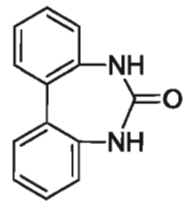
IV. Appendix

IV-1. NMR Spectras

IV-1.1. Biphenyl urea (3)



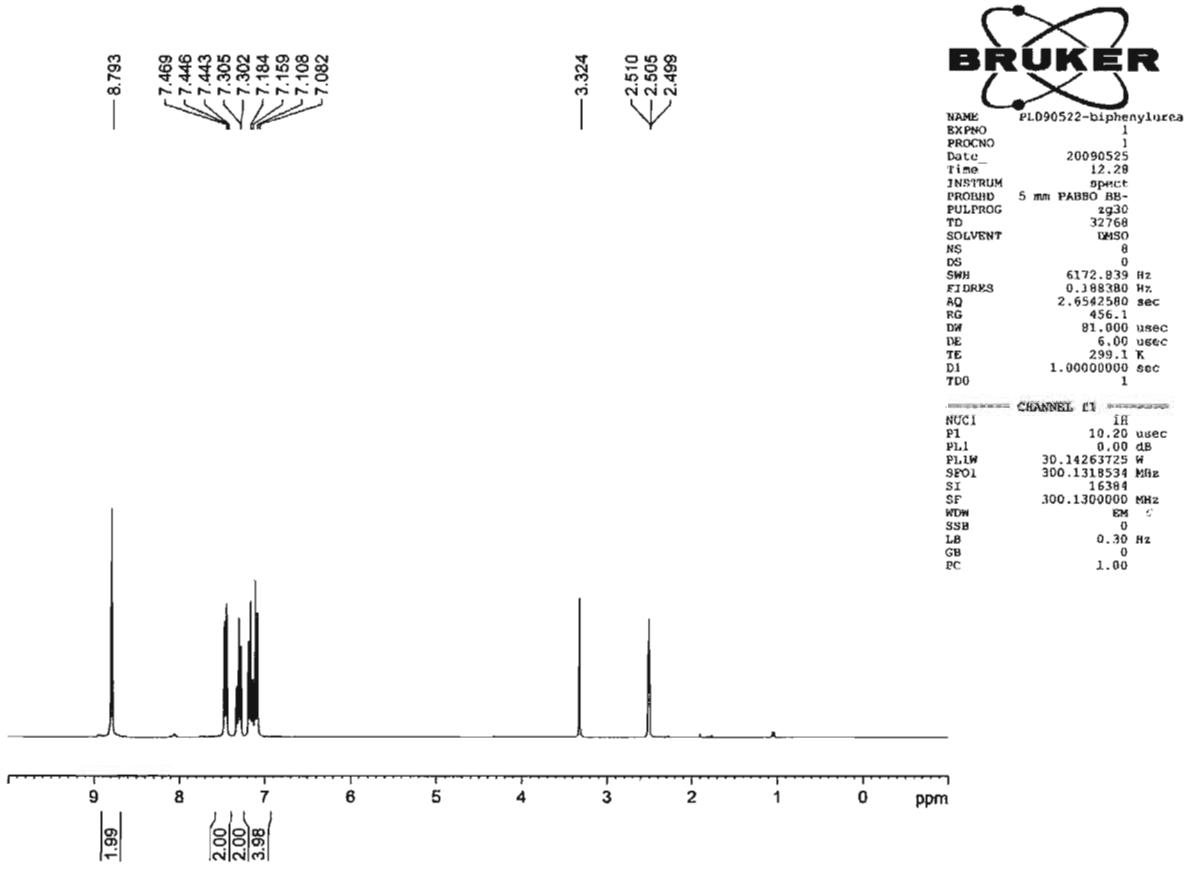


Figure IV-1: Biphenyl urea ^{1}H-NMR (DMSO, 300MHz)

IV-1.2. Dimethylbiphenyl urea (4)

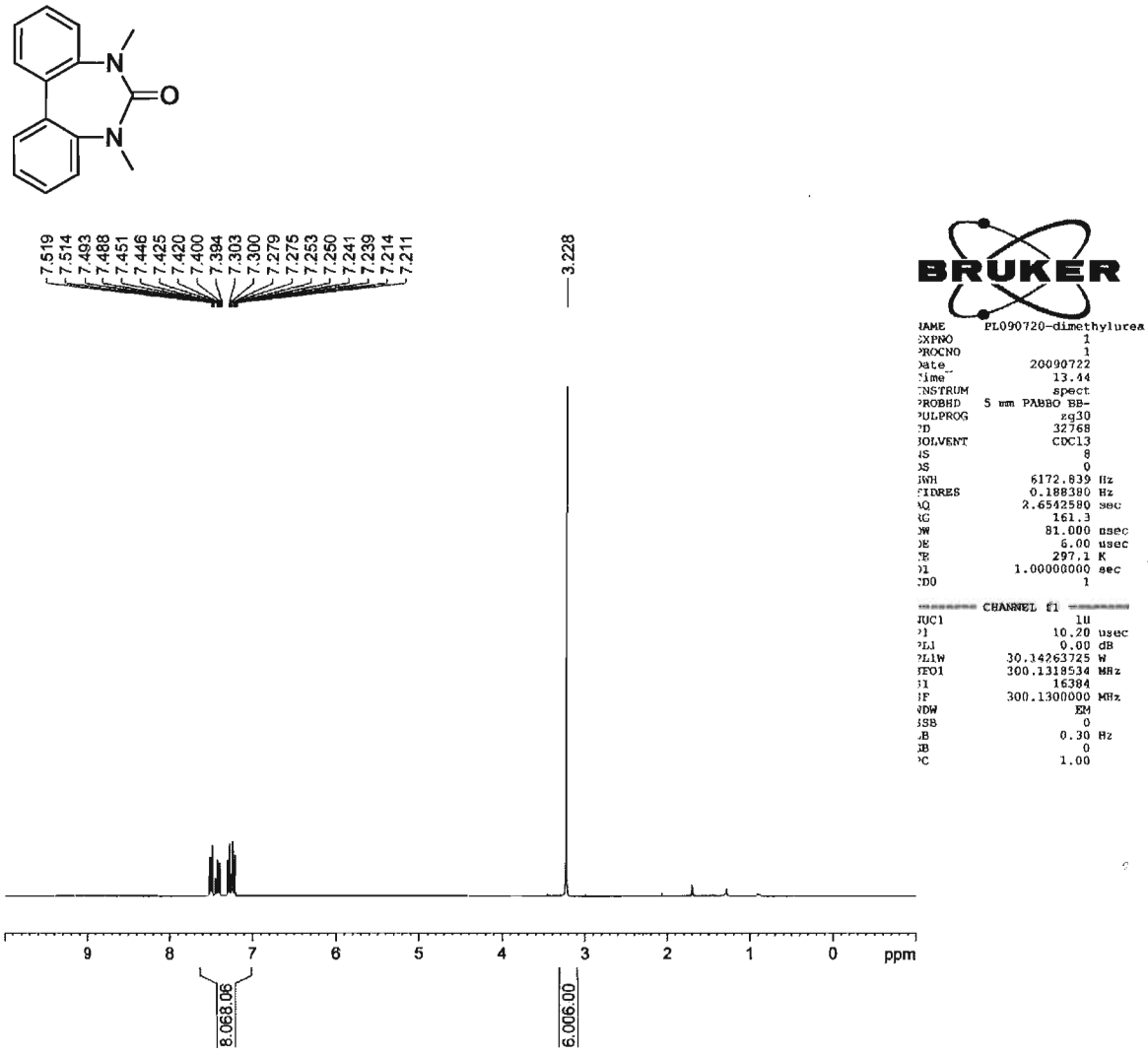


Figure IV-2: Dimethylbiphenyl urea ^{1}H-NMR ($CDCl_3$, 300MHz).

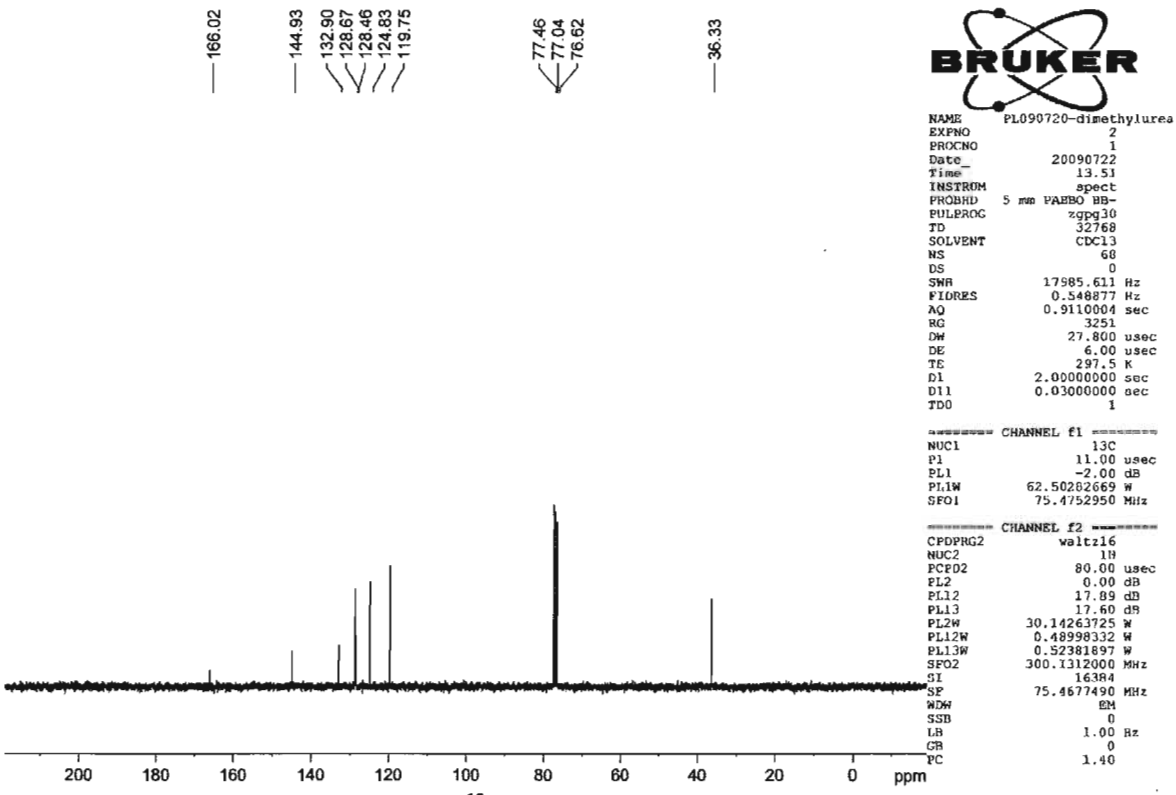


Figure IV-3: Dimethylbiphenyl urea ^{13}C-NMR ($CDCl_3$, 300MHz).

IV-1.3. 6-chloro-5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-7-ium chloride (5):

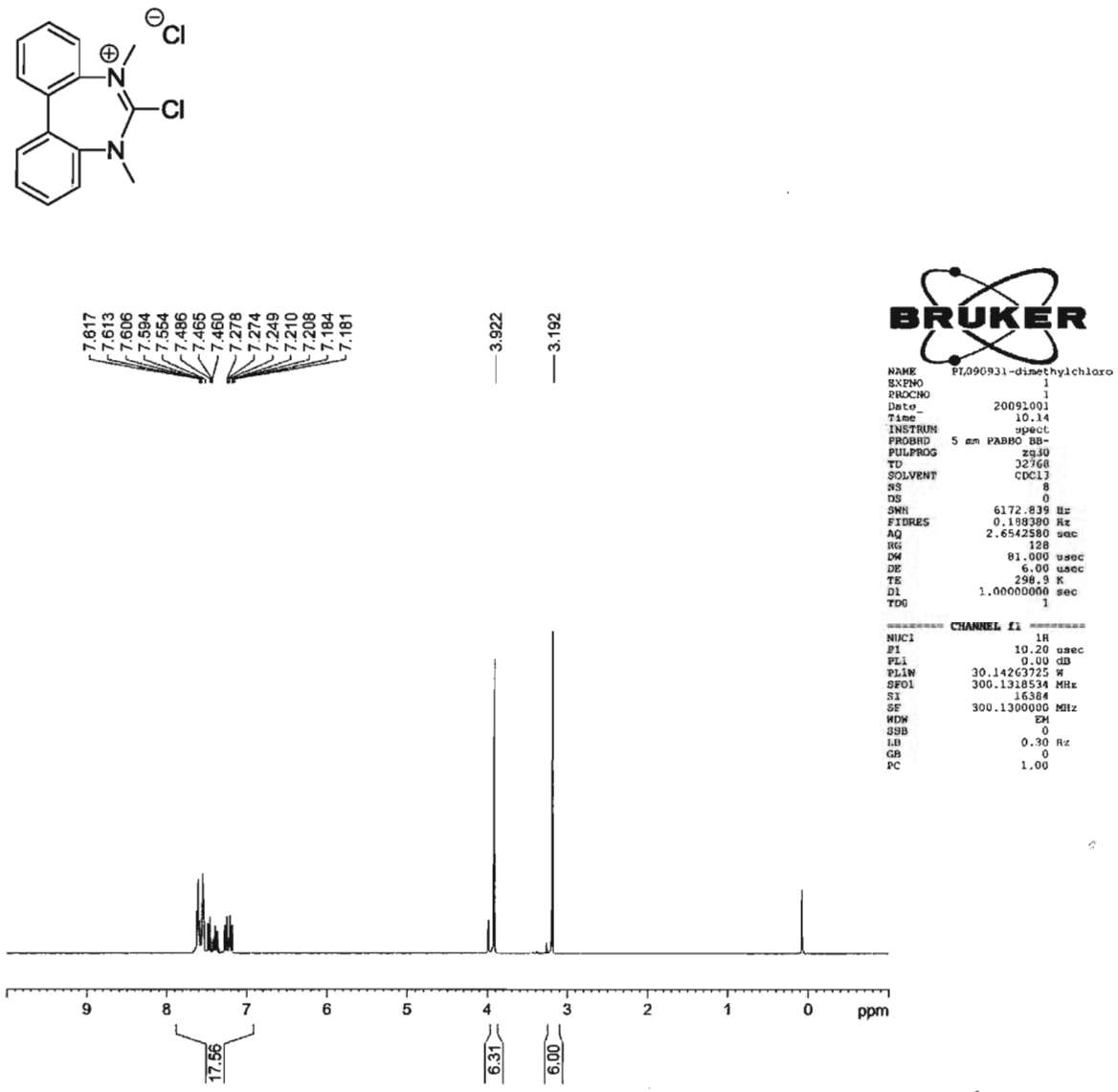
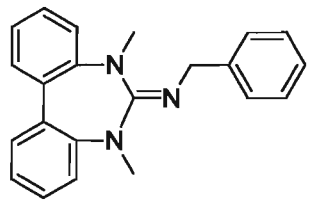


Figure IV-4: 6-chloro-5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-7-ium chloride ^{1}H-NMR ($CDCl_3$).

IV-1.4. *N*-(5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-1-phenylmethanamine (7)



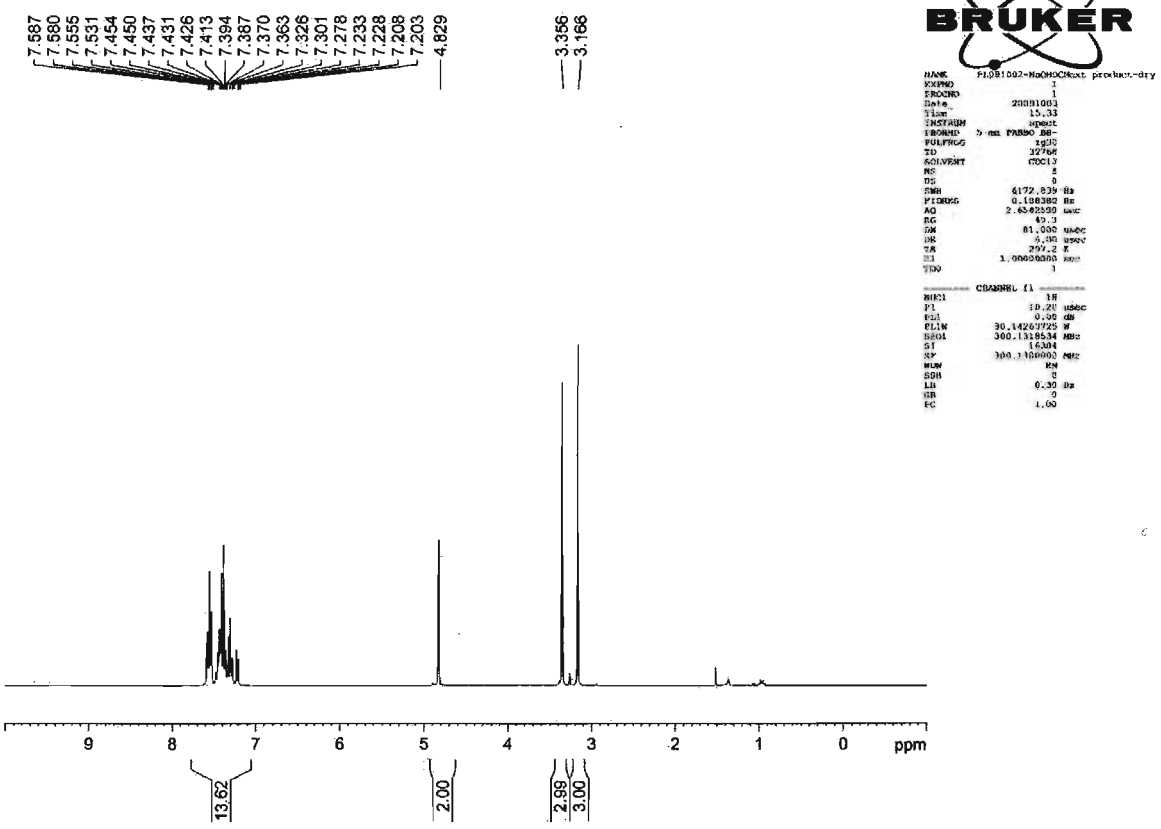


Figure IV-5: *N*-(5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-1-phenylmethanamine ^{1}H-NMR ($CDCl_3$).

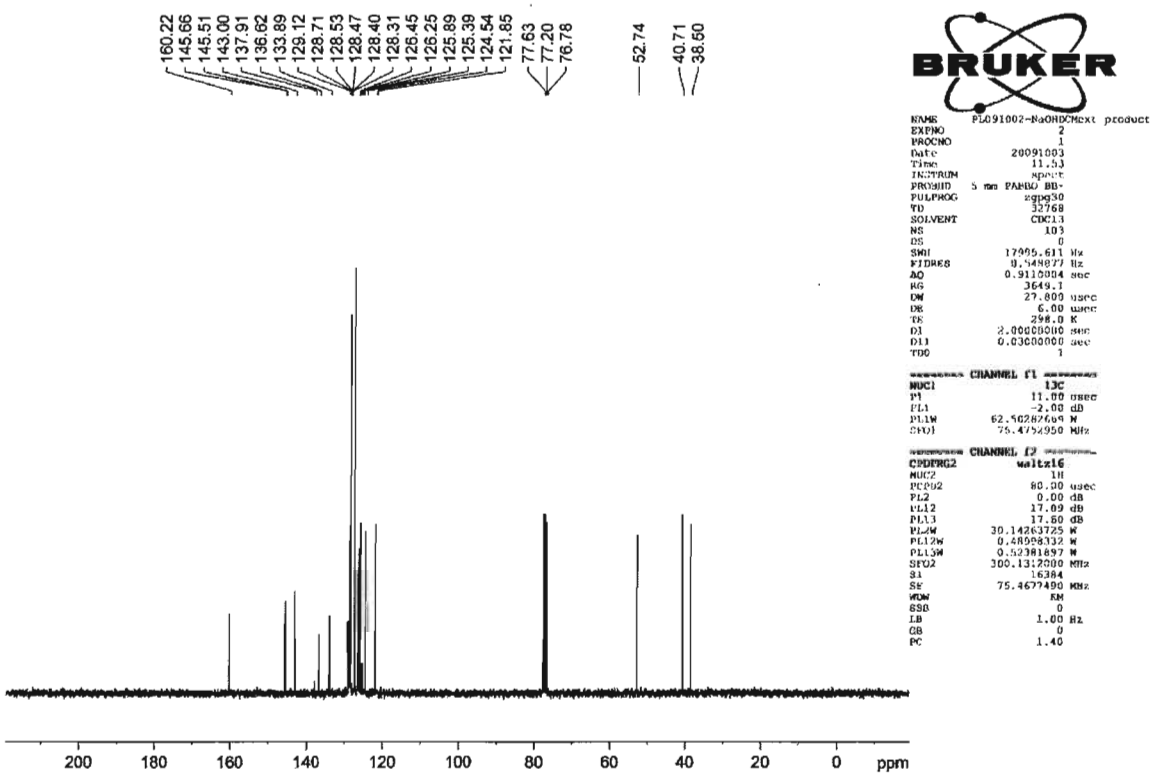


Figure IV-6: *N*-(5,7-dimethyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-1-phenylmethanamine ^{13}C-NMR ($CDCl_3$).

IV-1.5. 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-one (10)

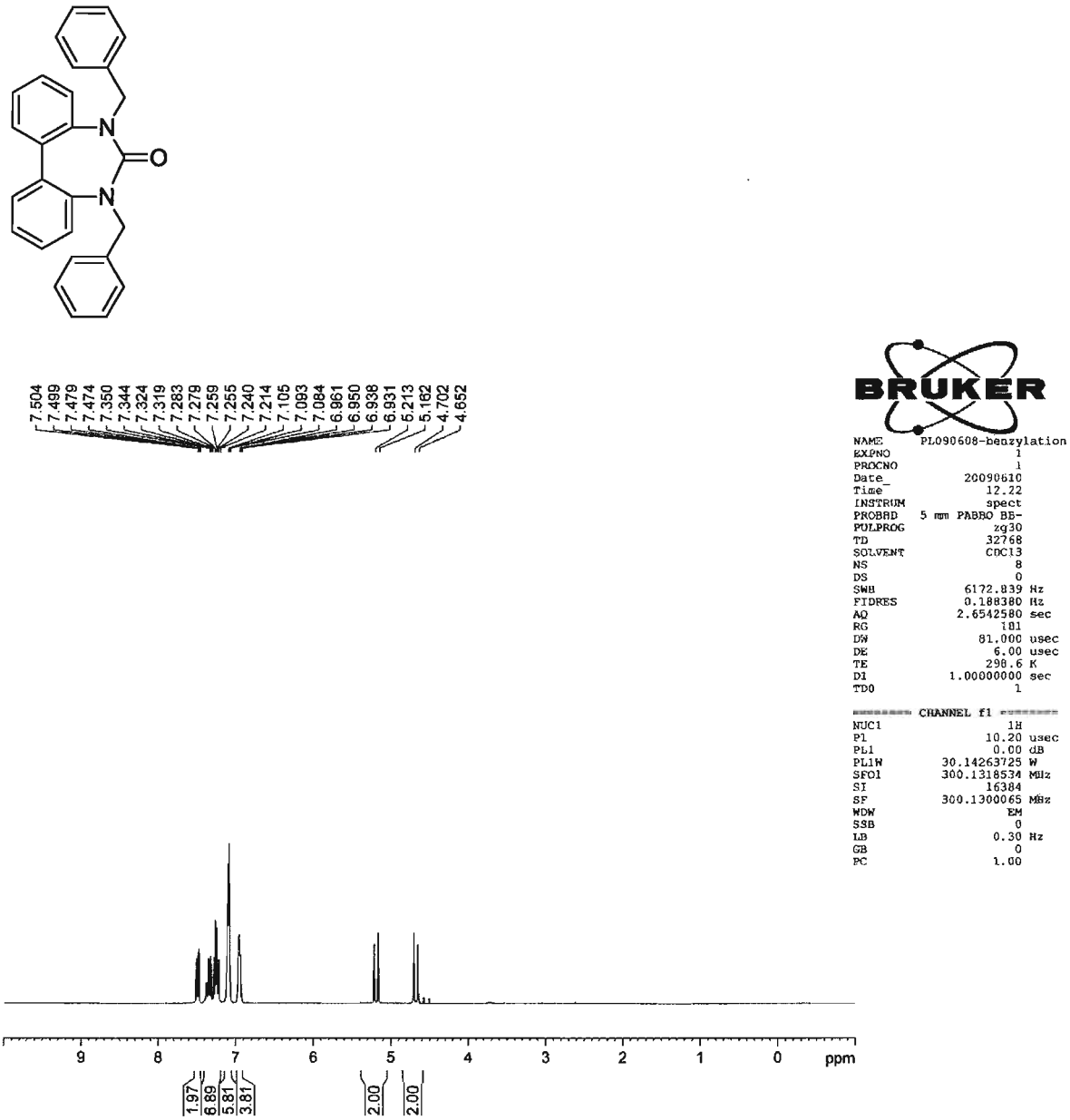
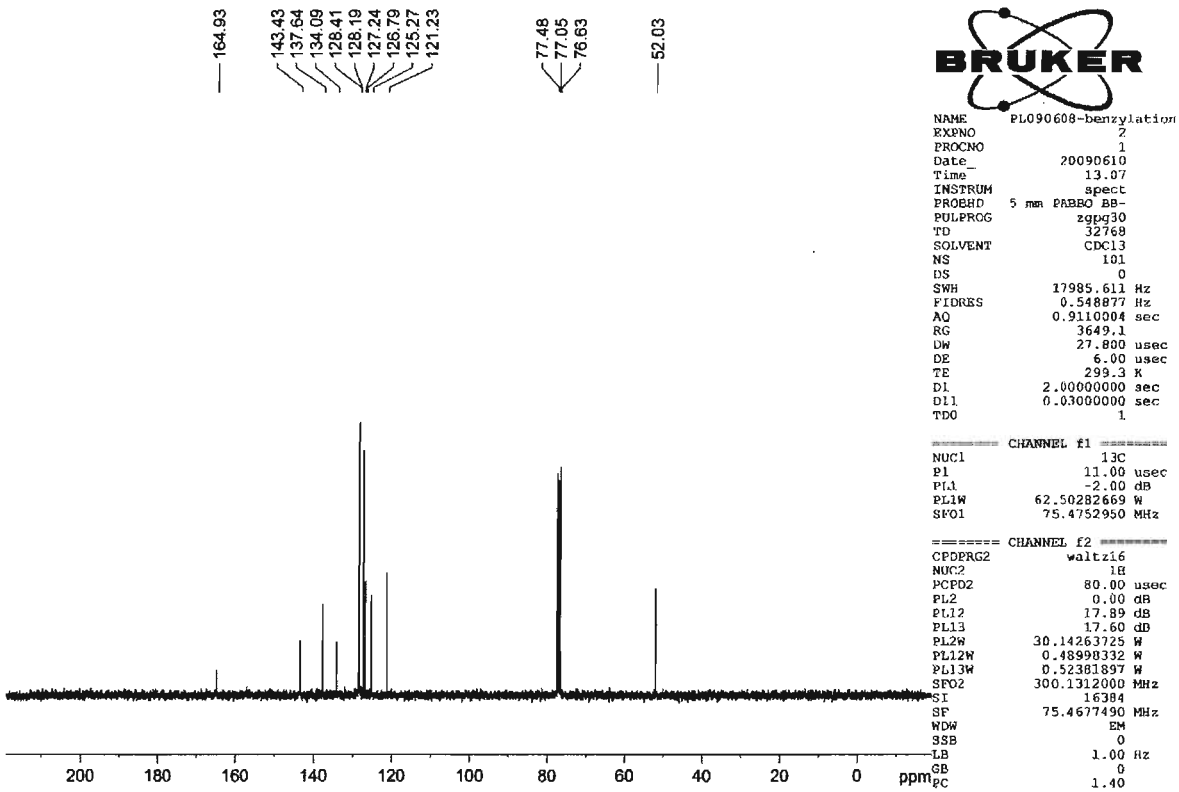


Figure IV-7: 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-one ^{1}H-NMR ($CDCl_3$).



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PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	101
DS	0
SWH	17985.611 Hz
FIDRES	0.548877 Hz
AQ	0.9110004 sec
RG	3649.1
DW	27.800 usec
DE	6.00 usec
TE	299.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	11.00 usec
PL1	-2.00 dB
PL1W	62.50282669 W
SFO1	75.4752950 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	0.00 dB
PL12	17.89 dB
PL13	17.60 dB
PL2W	30.14263725 W
PL12W	0.48998332 W
PL13W	0.52381897 W
SFO2	300.1312000 MHz
SI	16384
SF	75.4677490 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

Figure IV-8: : 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepin-6(7H)-one ^{13}C-NMR ($CDCl_3$).

IV-1.6. 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepine-6(7H)-thione (11)

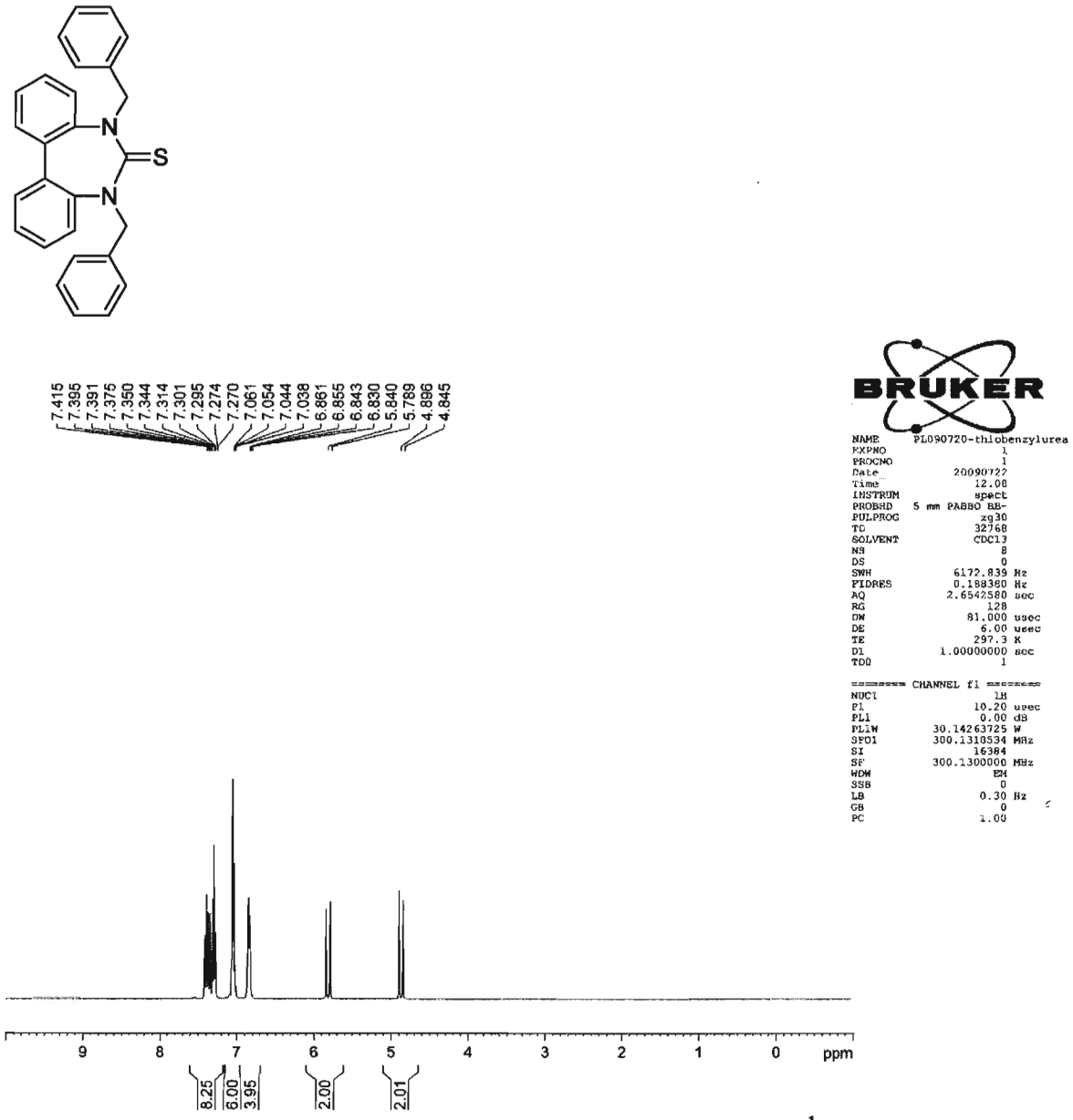


Figure IV-9: 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepine-6(7H)-thione ^{1}H-NMR ($CDCl_3$).

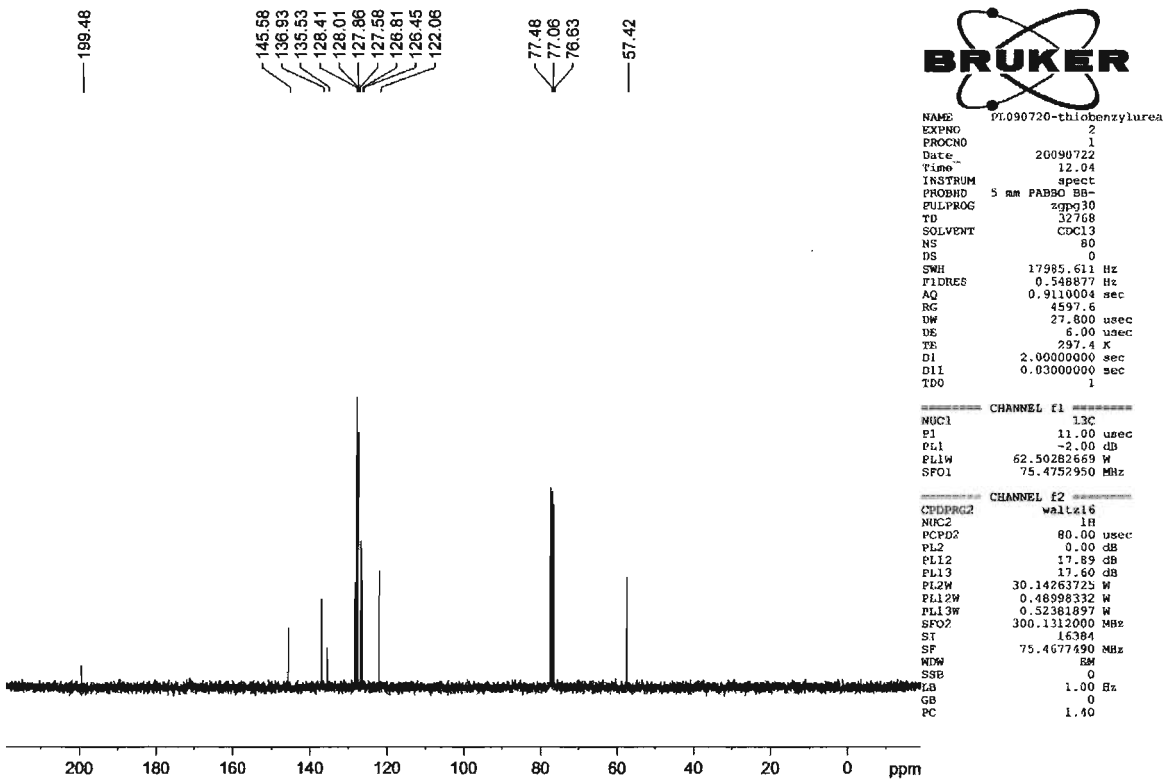
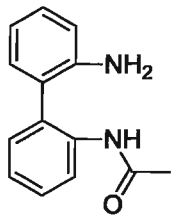
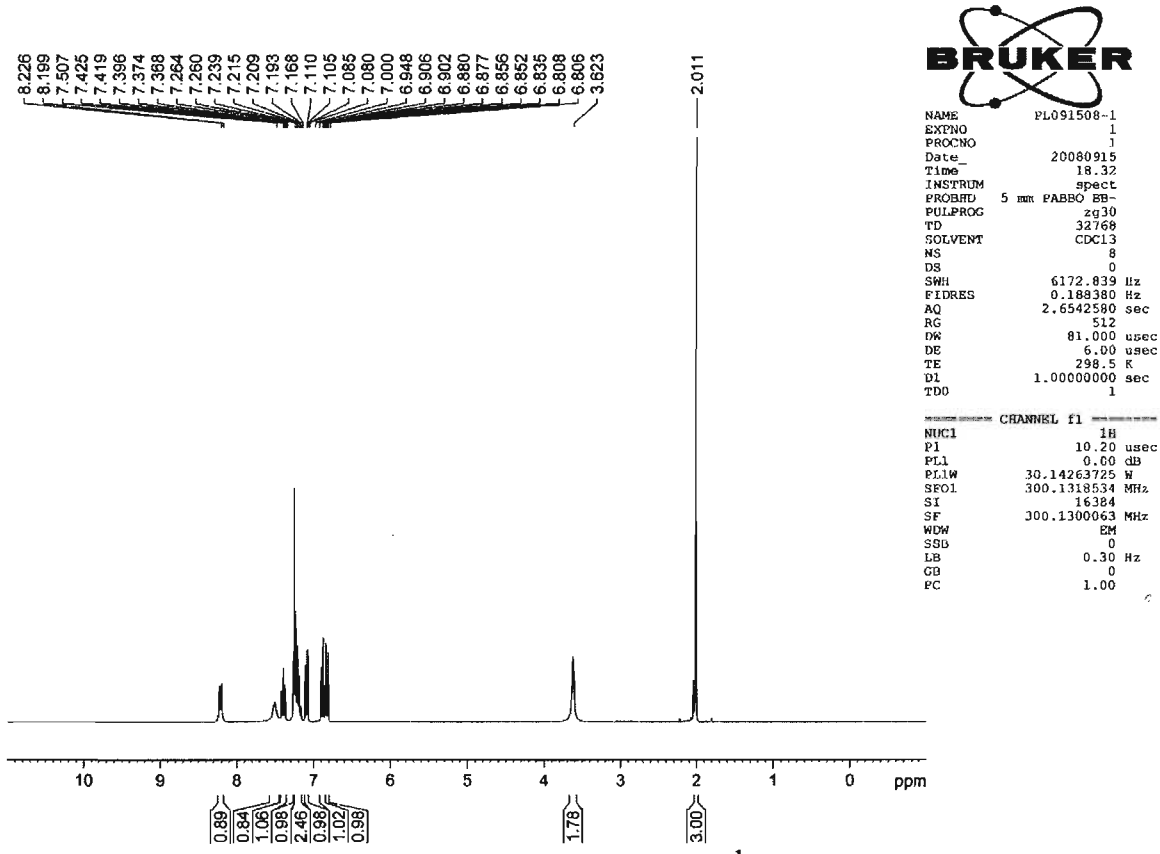


Figure IV-10: 5,7-dibenzyl-5H-dibenzo[d,f][1,3]diazepine-6(7H)-thione ^{13}C-NMR ($CDCl_3$).

IV-1.7. *N*-(2'-amino-[1,1'-biphenyl]-2-yl)acetamide (14)





BRUKER

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TD	32768
SOLVENT	CDCl3
NS	8
DS	0
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	512
DW	81.000 usec
DE	6.00 usec
TE	298.5 K
D1	1.00000000 sec
TD0	1
====== CHANNEL f1 ======	
NUC1	1H
P1	10.20 usec
PL1	0.00 dB
PL1W	30.14263725 W
SFO1	300.1318534 MHz
SI	16384
SF	300.1300063 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Figure IV-11: *N*-(2'-amino-[1,1'-biphenyl]-2-yl)acetamide ^{1}H-NMR ($CDCl_3$).

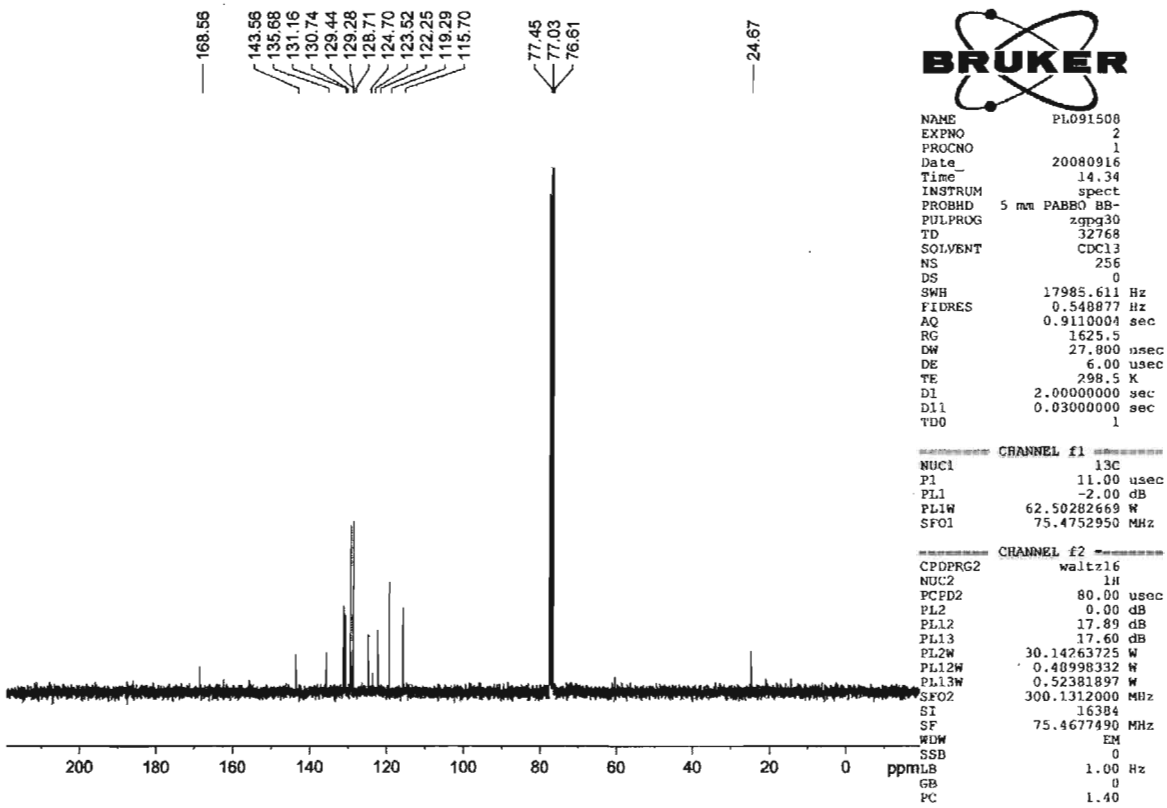
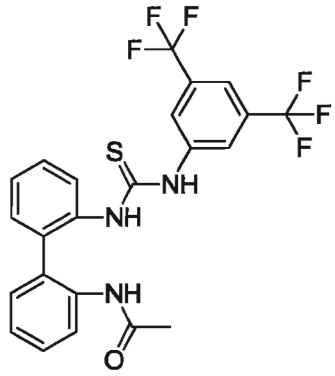
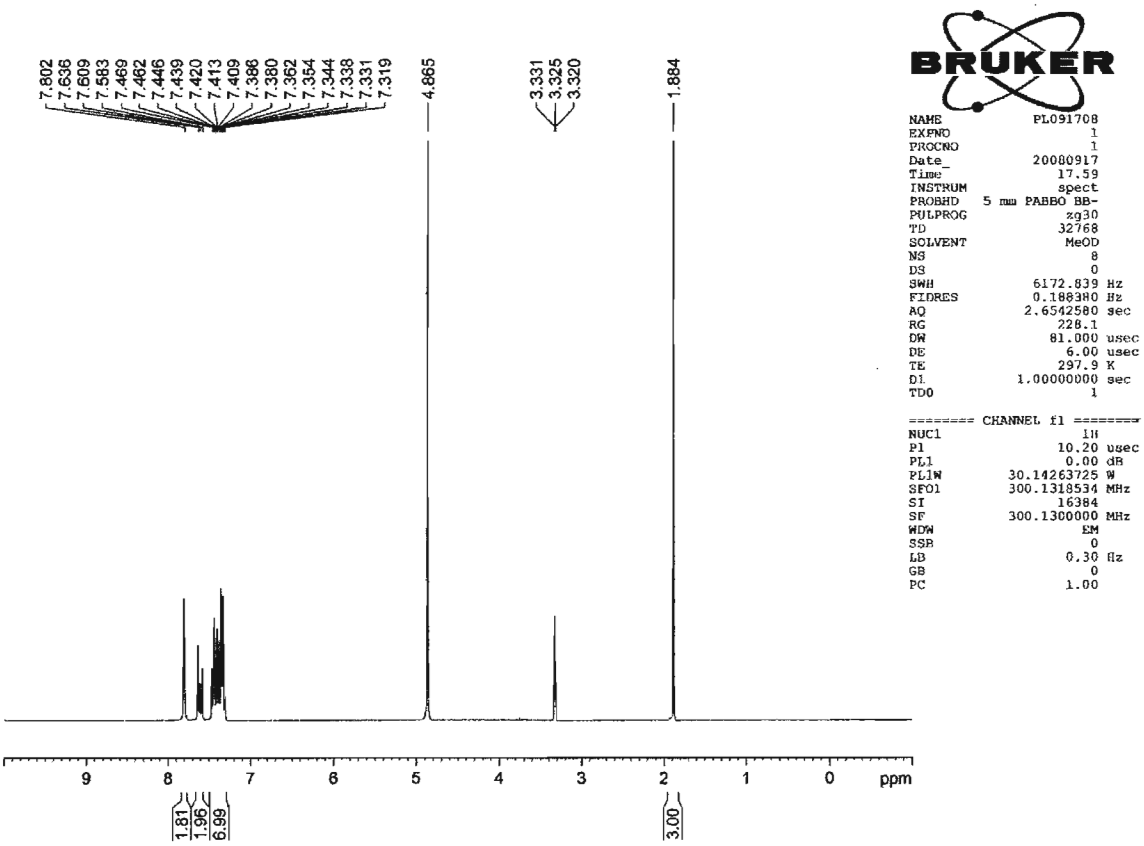


Figure IV-12: *N*-(2'-amino-[1,1'-biphenyl]-2-yl)acetamide ^{13}C-NMR ($CDCl_3$).

IV-1.8. N-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)acetamide (16)





BRUKER

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PULPROG	zg30
TD	32768
SOLVENT	MeOD
NS	8
DS	0
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	228.1
DW	81.000 usec
DE	6.00 usec
TE	297.9 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.20 usec
PL1	0.00 dB
PL1W	30.14263725 W
SFO1	300.1318534 MHz
SI	16384
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Figure IV-13: *N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)acetamide ^{1}H-NMR ($CDCl_3$).

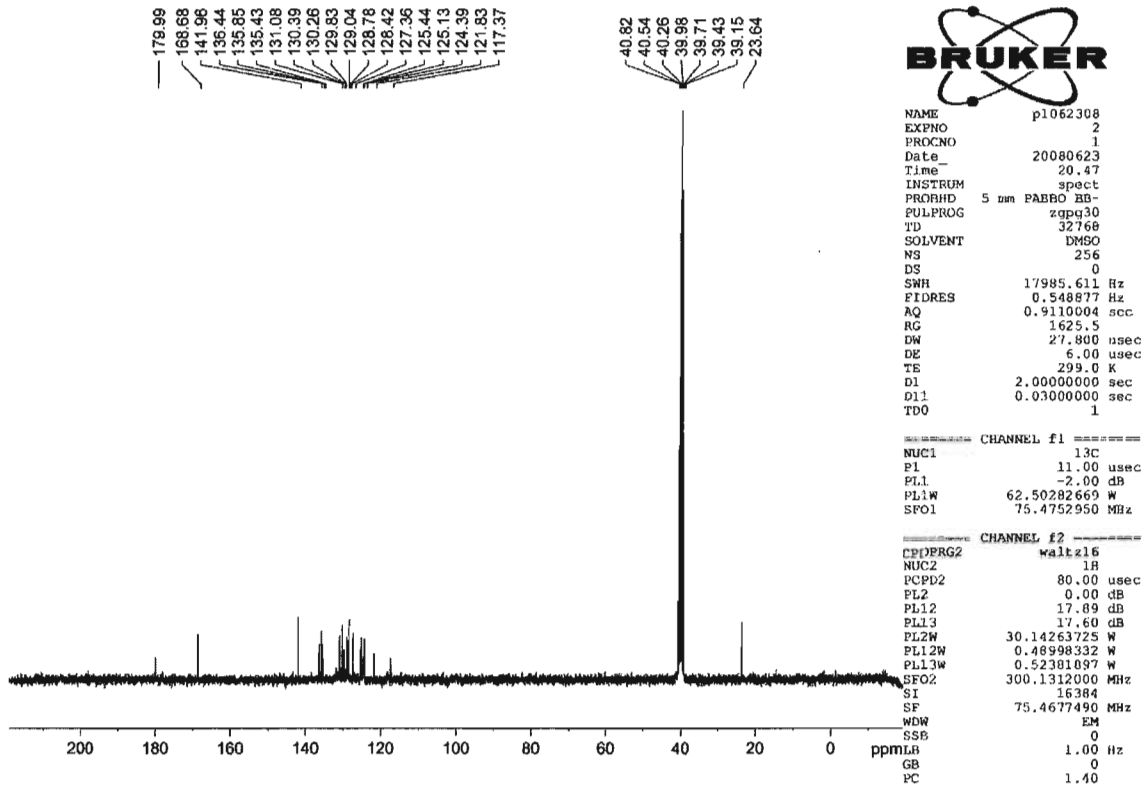
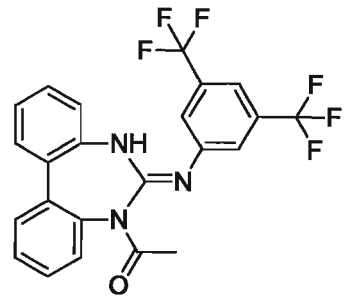


Figure IV-14: *N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-[1,1'-biphenyl]-2-yl)acetamide ^{13}C-NMR ($CDCl_3$).

IV-1.9. 1-(6-((3,5-bis(trifluoromethyl)phenyl)imino)-6,7-dihydro-5H-dibenzo[d,f]-[1,3]diazepin-5-yl)ethanone (18)



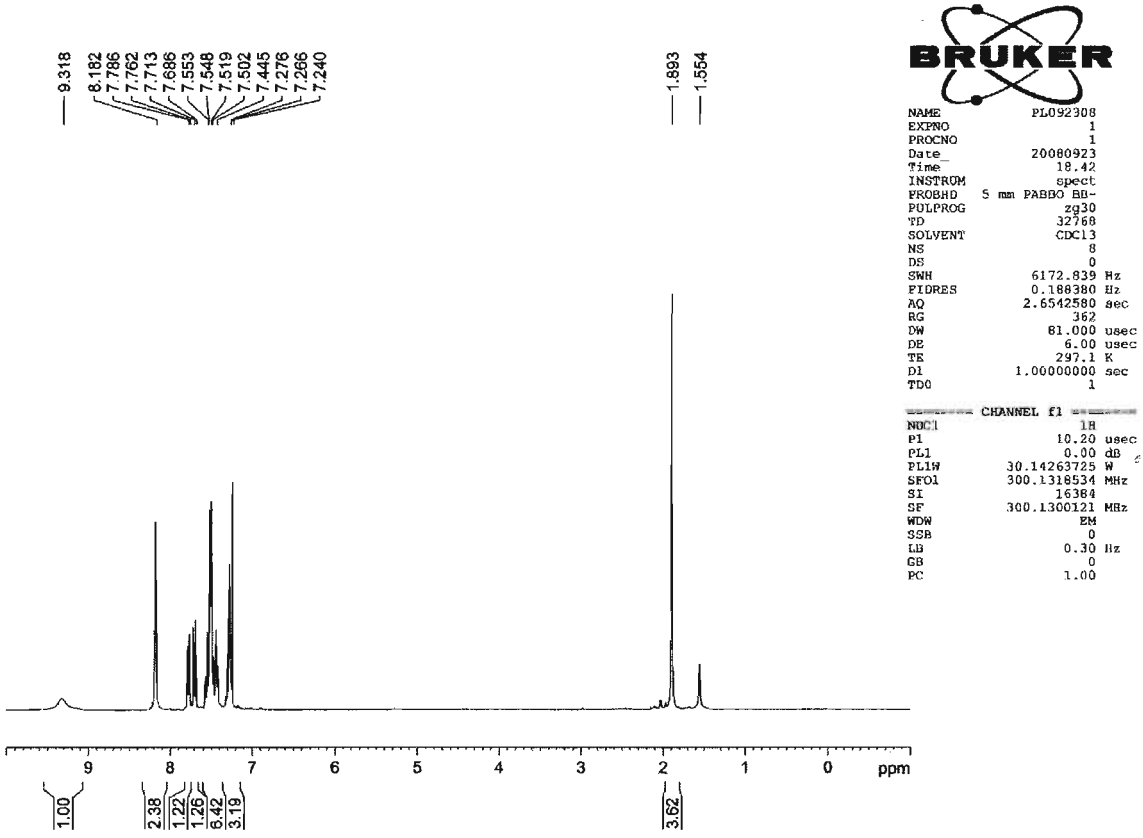


Figure IV-15: 1-(6-((3,5-bis(trifluoromethyl)phenyl)imino)-6,7-dihydro-5H-dibenzo[d,f][1,3] diazepin-5-yl)ethanone ^{1}H-NMR ($CDCl_3$).

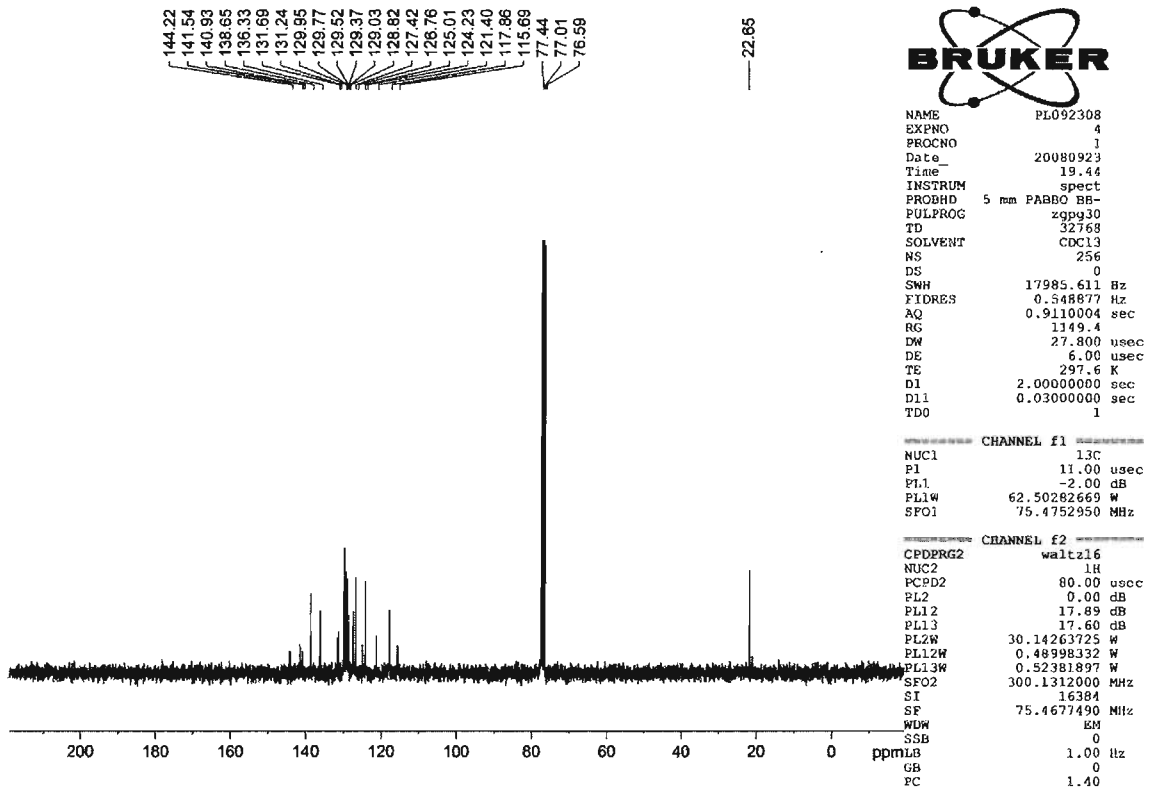


Figure IV-16: 1-(6-((3,5-bis(trifluoromethyl)phenyl)imino)-6,7-dihydro-5H-dibenzo[d,f][1,3] diazepin-5-yl)ethanone ^{13}C-NMR ($CDCl_3$).

IV-1.10. *N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl) aniline (19)

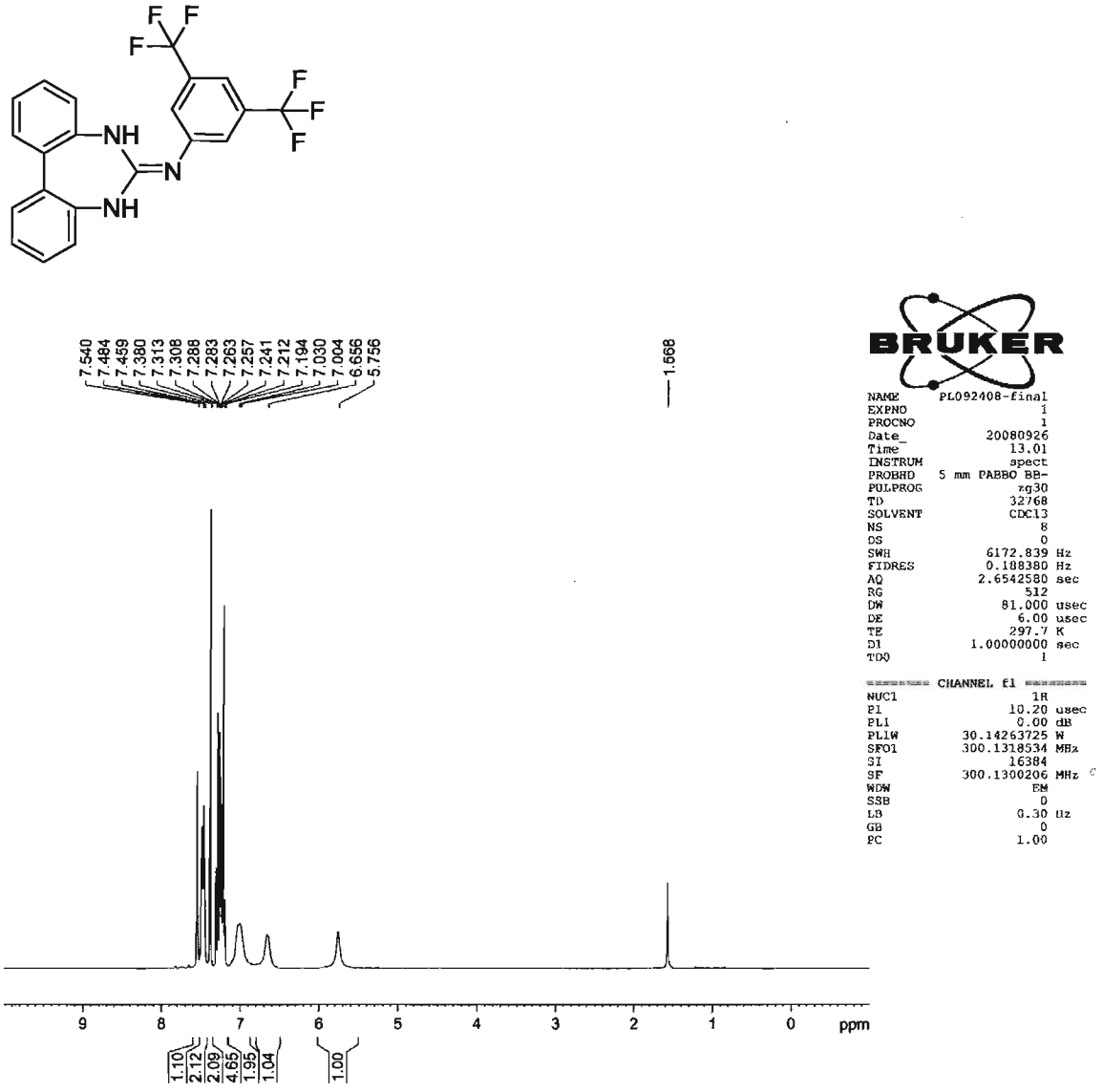


Figure IV-17: *N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl)aniline ^{1}H-NMR ($CDCl_3$).

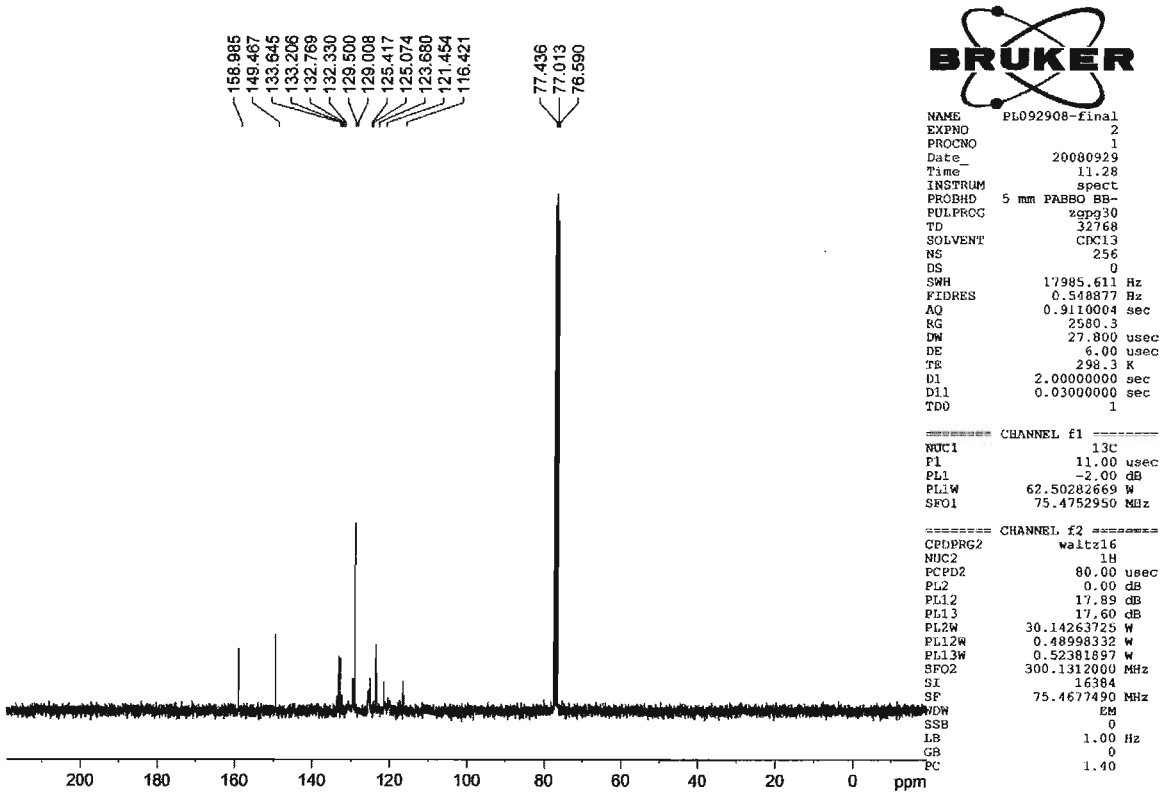
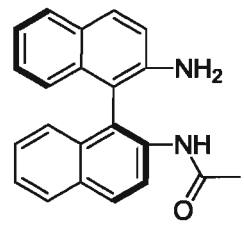


Figure IV-18: *N*-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3,5-bis(trifluoromethyl)aniline ^{13}C-NMR ($CDCl_3$).

IV-1.11. (*S*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl) acetamide



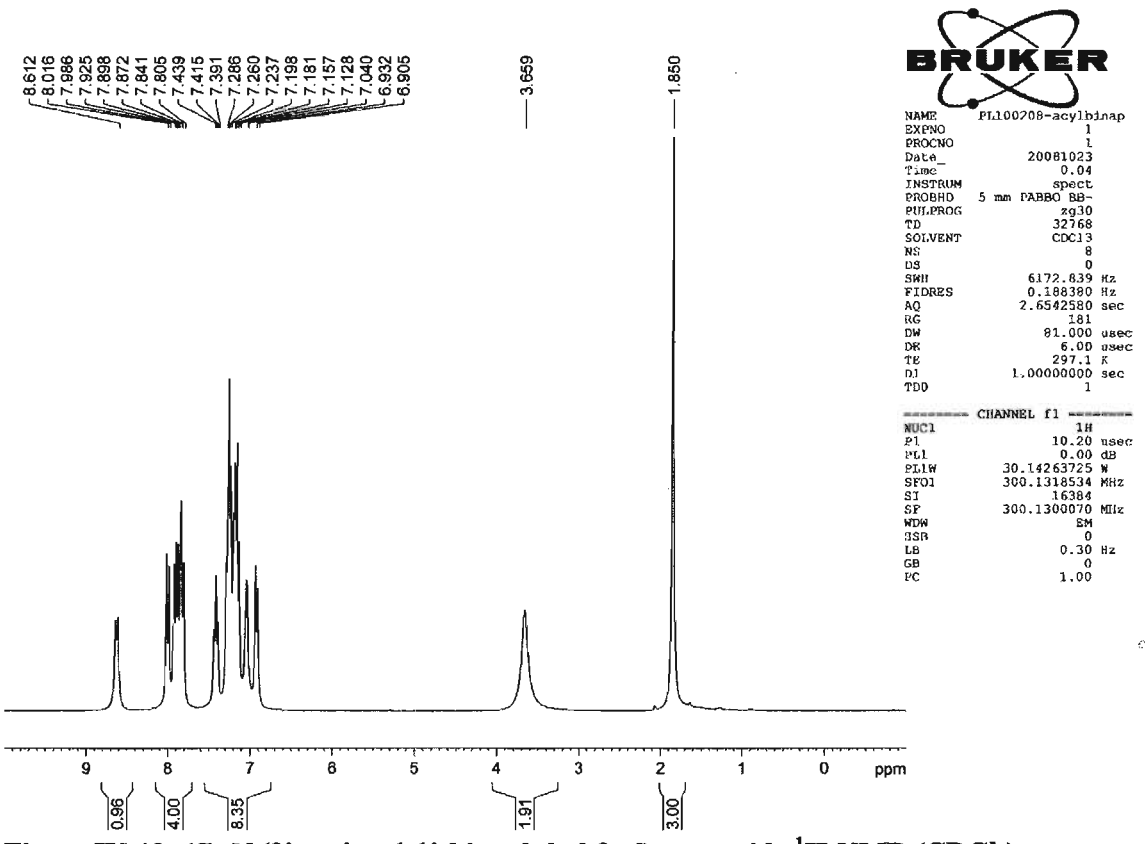


Figure IV-19: (*S*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl) acetamide ^{1}H-NMR ($CDCl_3$)

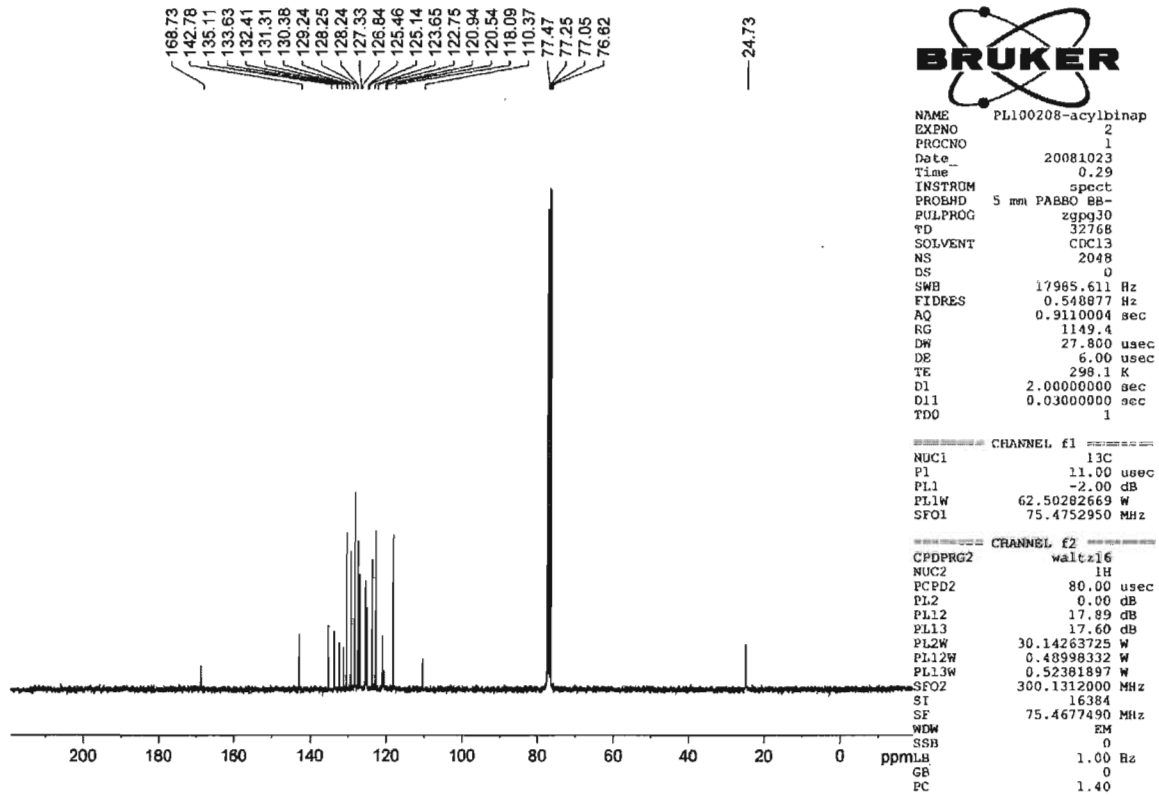
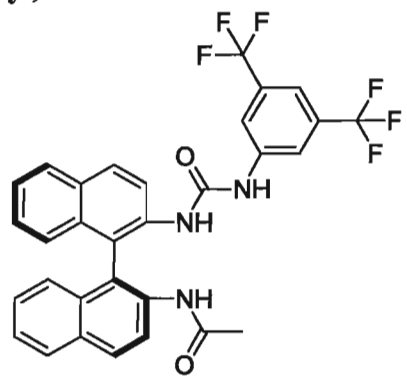


Figure IV-20: (*S*)-*N*-(2'-amino-1,1'-binaphthyl-2-yl) acetamide ^{13}C-NMR ($CDCl_3$).

IV-1.12. (*S*)-*N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-1,1'-binaphthyl-2-yl)acetamide



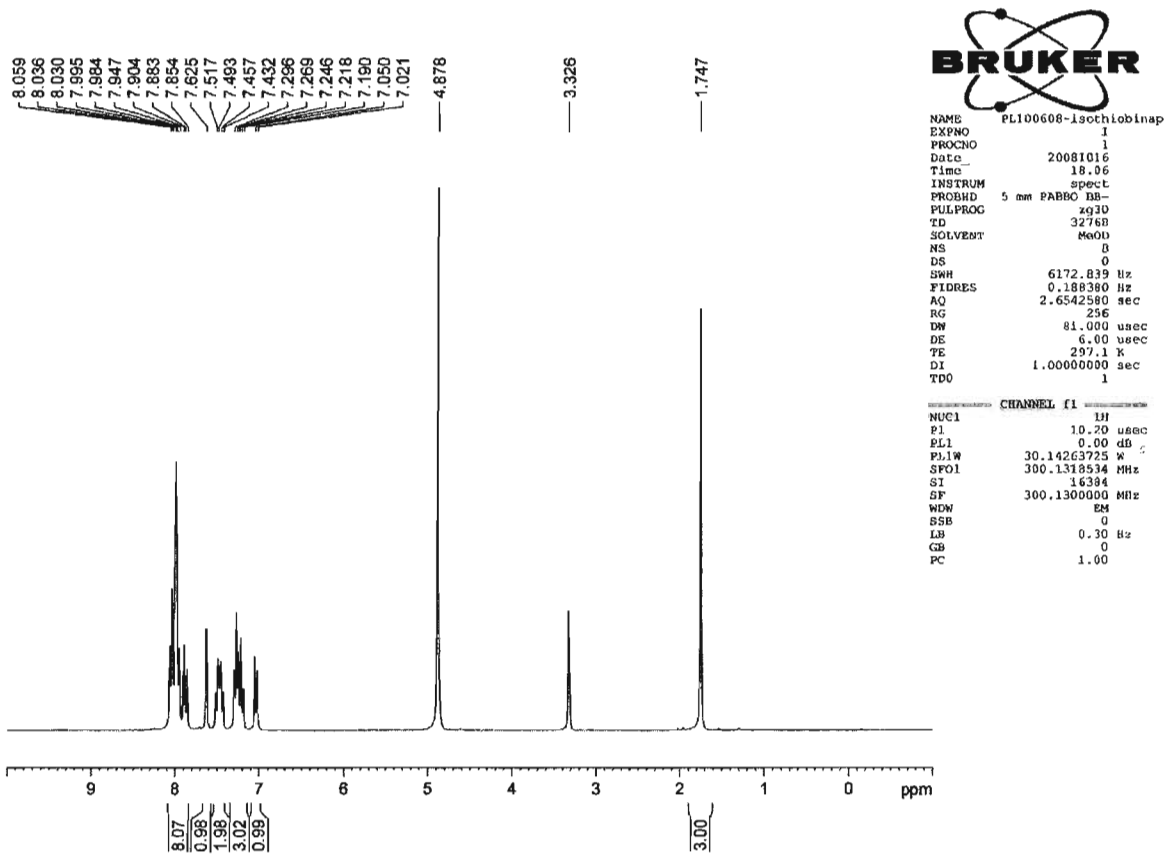


Figure IV-21: (*S*)-*N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-1,1'-binaphthyl-2-yl)acetamide ^{1}H-NMR ($CDCl_3$).

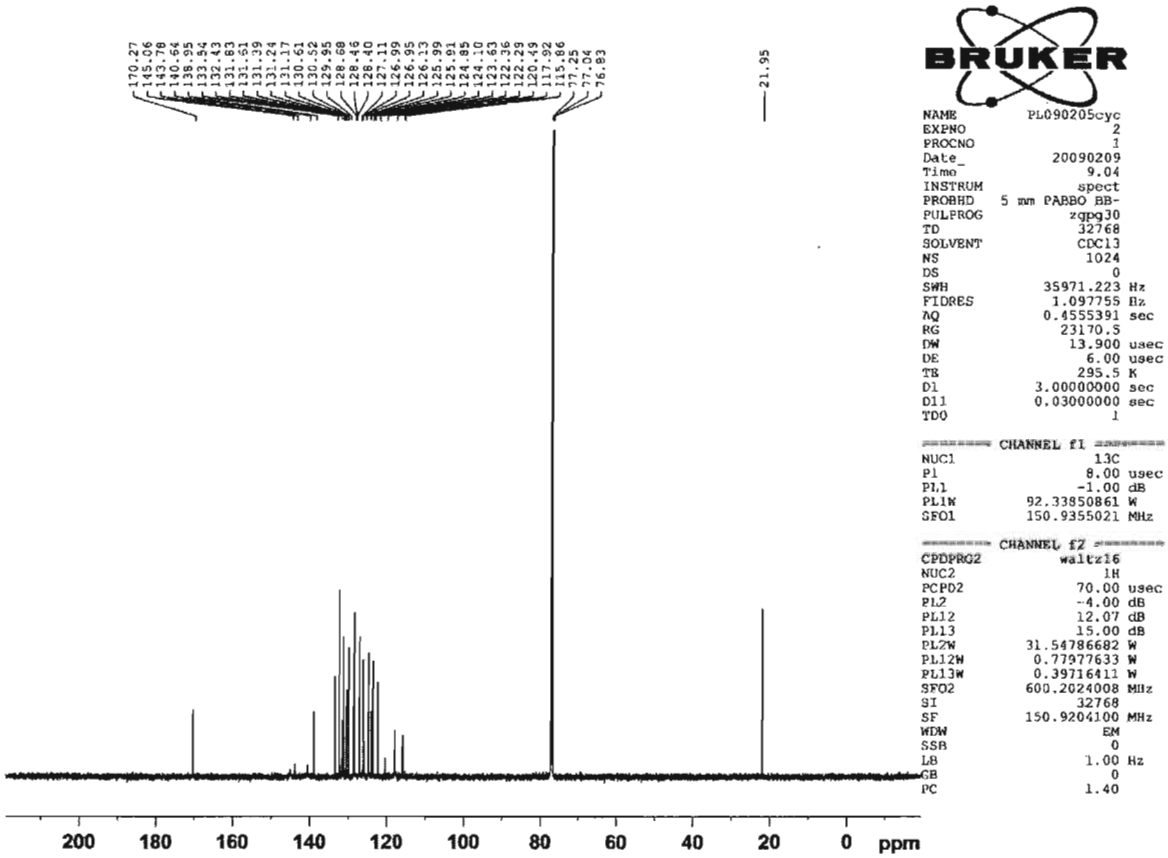
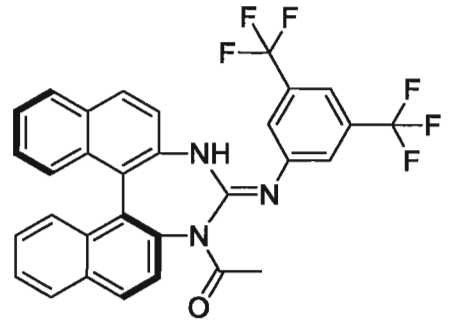
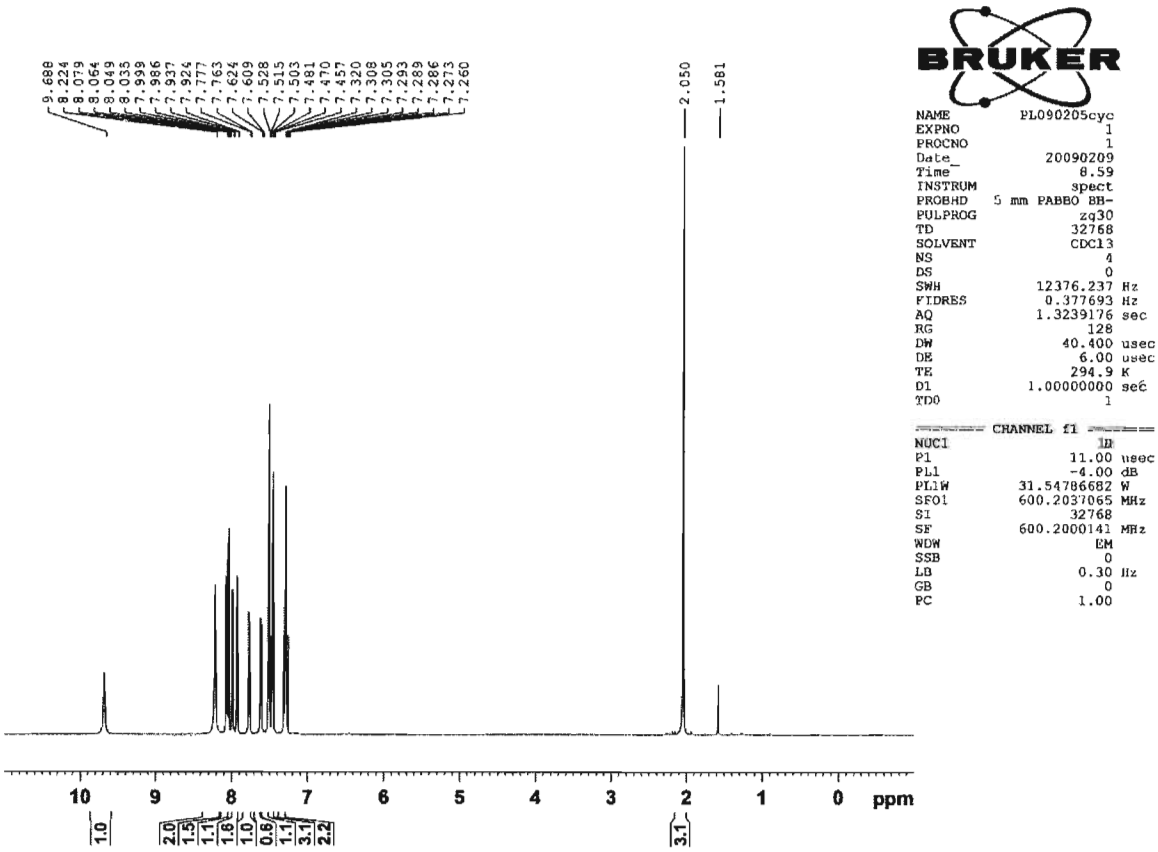


Figure IV-22: (*S*)-*N*-(2'-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-1,1'-binaphthyl-2-yl)acetamide ^{13}C-NMR ($CDCl_3$).

IV-1.13. (*S*)-1-(4-(3,5-bis(trifluoromethyl)phenylimino)-4,5-dihydro-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-3-yl)ethanone





BRUKER

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PROCNO	1
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PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	4
DS	0
SWH	12376.237 Hz
FIDRES	0.377693 Hz
AQ	1.3239176 sec
RG	128
DW	40.400 usec
DE	6.00 usec
TE	294.9 K
D1	1.00000000 sec
TD0	1
====== CHANNEL f1 ======	
NUC1	1H
P1	11.00 usec
PL1	-4.00 dB
PL1W	31.54786682 W
SFO1	600.2037065 MHz
SI	32768
SF	600.2000141 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Figure IV-23: (*S*)-1-(4-(3,5-bis(trifluoromethyl)phenylimino)-4,5-dihydro-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-3-yl)ethanone ^{1}H-NMR (600MHz, $CDCl_3$).

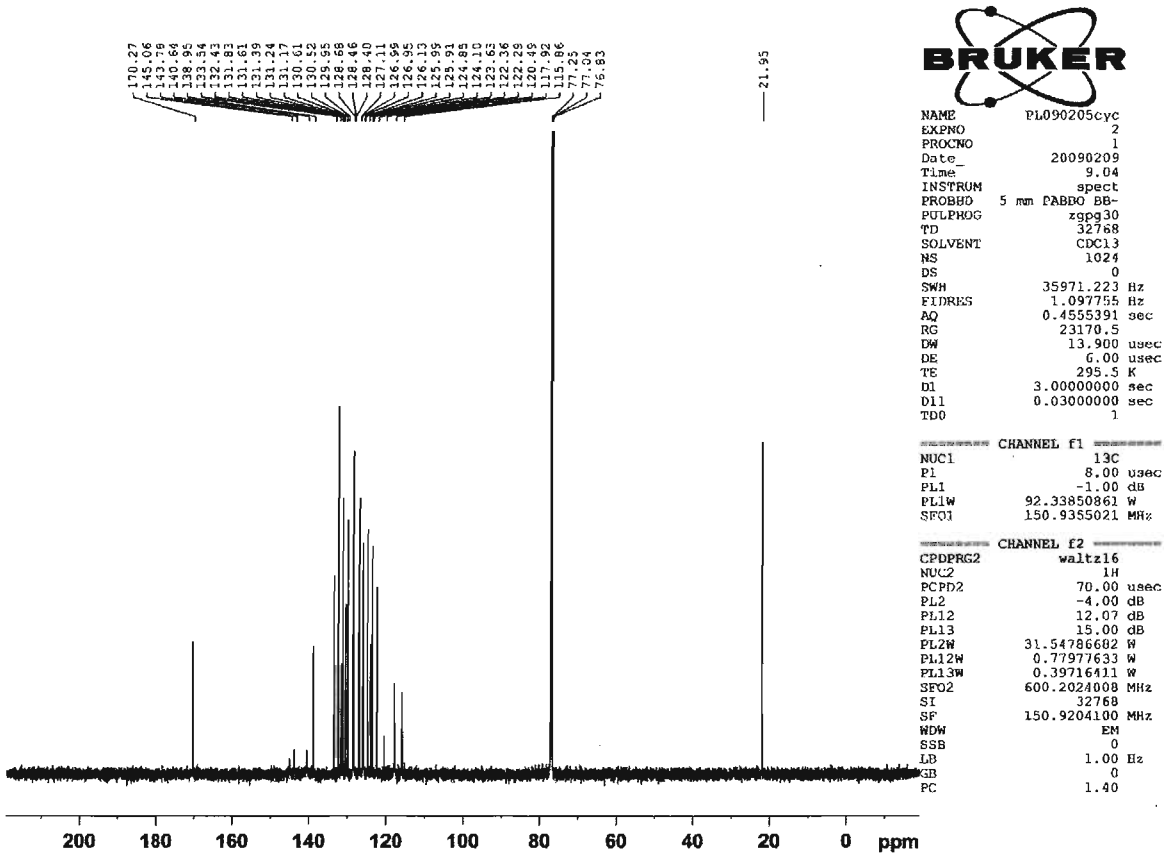
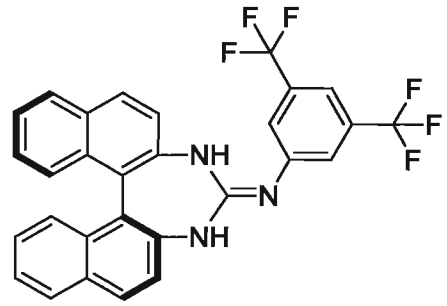
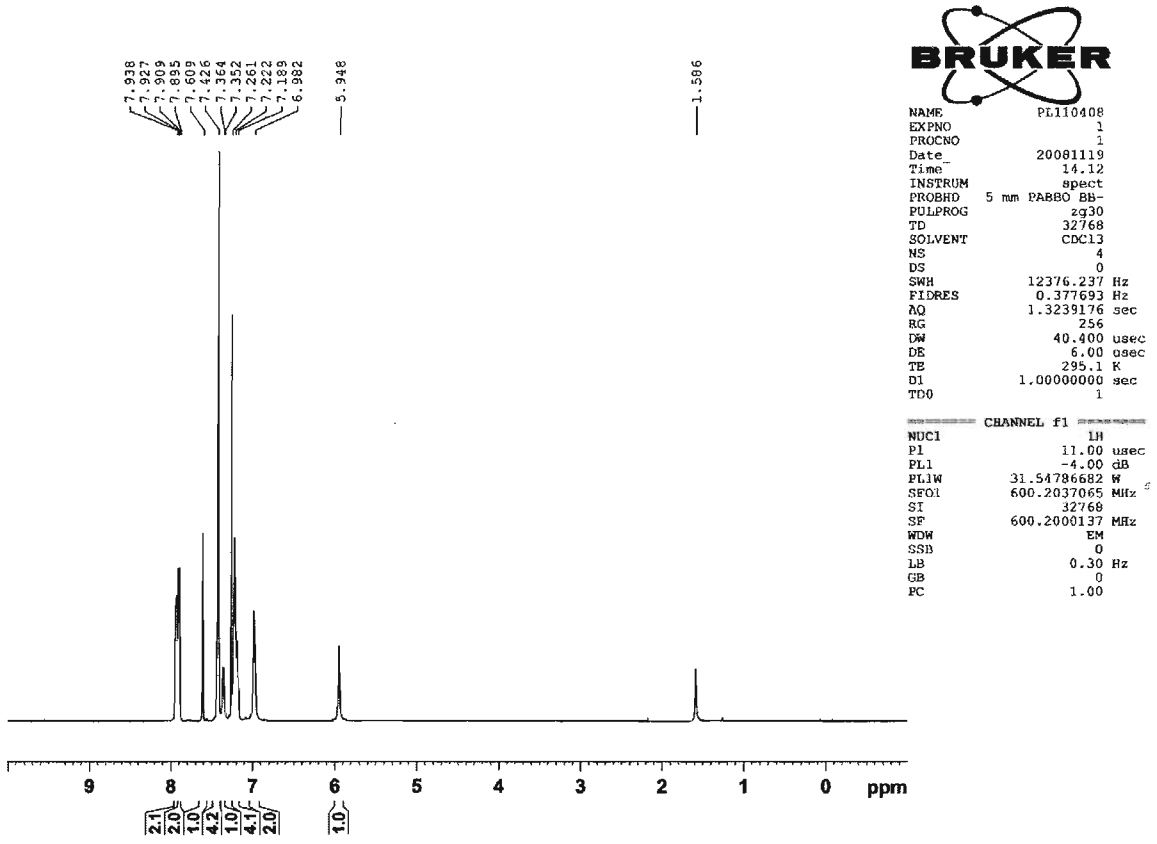


Figure IV-24: (*S*)-1-(4-(3,5-bis(trifluoromethyl)phenylimino)-4,5-dihydro-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-3-yl)ethanone ^{13}C-NMR (600MHz, $CDCl_3$).

IV-1.14. (*S*)-*N*-(3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)-3,5-bis (trifluoromethyl)aniline (21)





BRUKER

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RG	256
DW	40.400 usec
DE	6.00 usec
TE	295.1 K
D1	1.00000000 sec
TD0	1
CHANNEL f1	
NUC1	1H
P1	11.00 usec
PL1	-4.00 dB
PL1W	31.54786682 W
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SI	32768
SF	600.2000137 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Figure IV-25: (*S*)-*N*-(3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)-3,5-bis (trifluoromethyl)aniline ^{1}H-NMR (600MHz, $CDCl_3$).

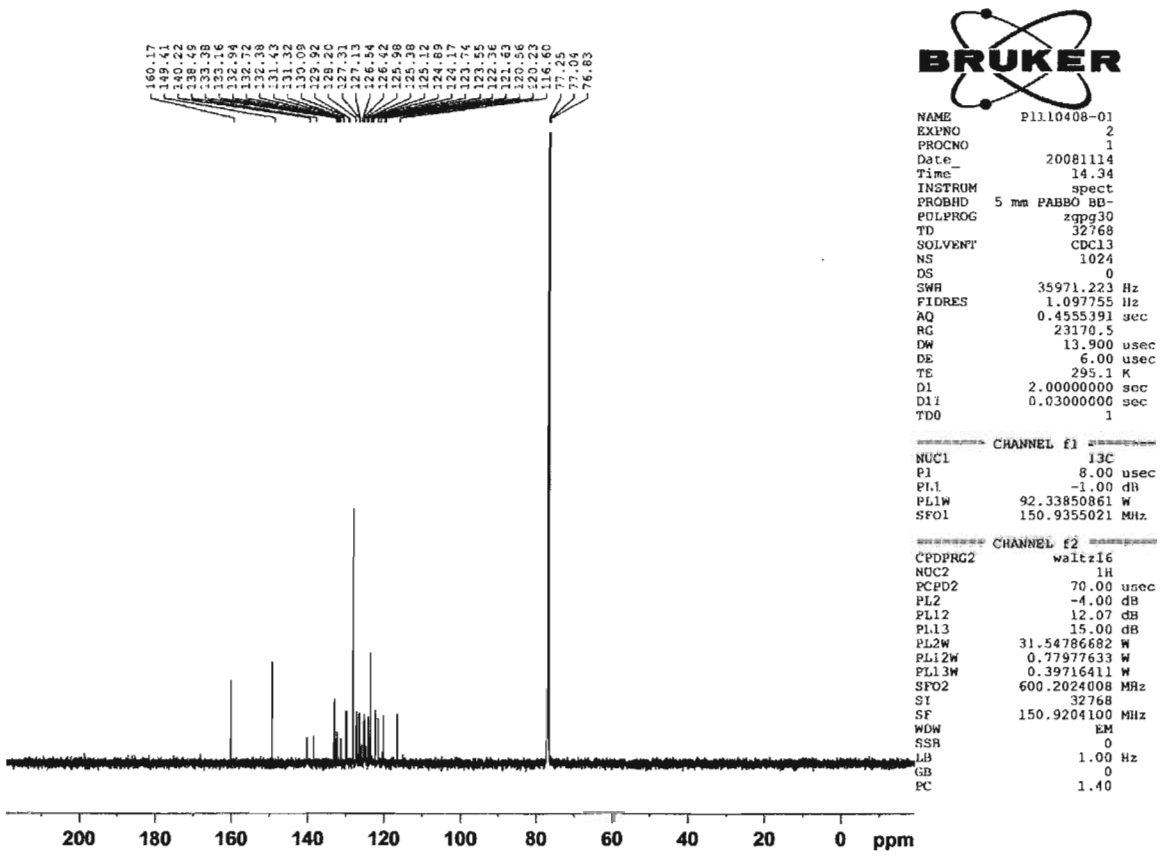


Figure IV-26: (*S*)-*N*-(3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)-3,5-bis (trifluoromethyl)aniline ^{13}C-NMR (600MHz, $CDCl_3$).

IV-1.15. (*R*)-1-(2'-amino-[1,1'-biphenyl]-2-yl)-3-(1-((tert-butyldimethylsilyl)oxy)-3-phenylpropan-2-yl)thiourea (27)

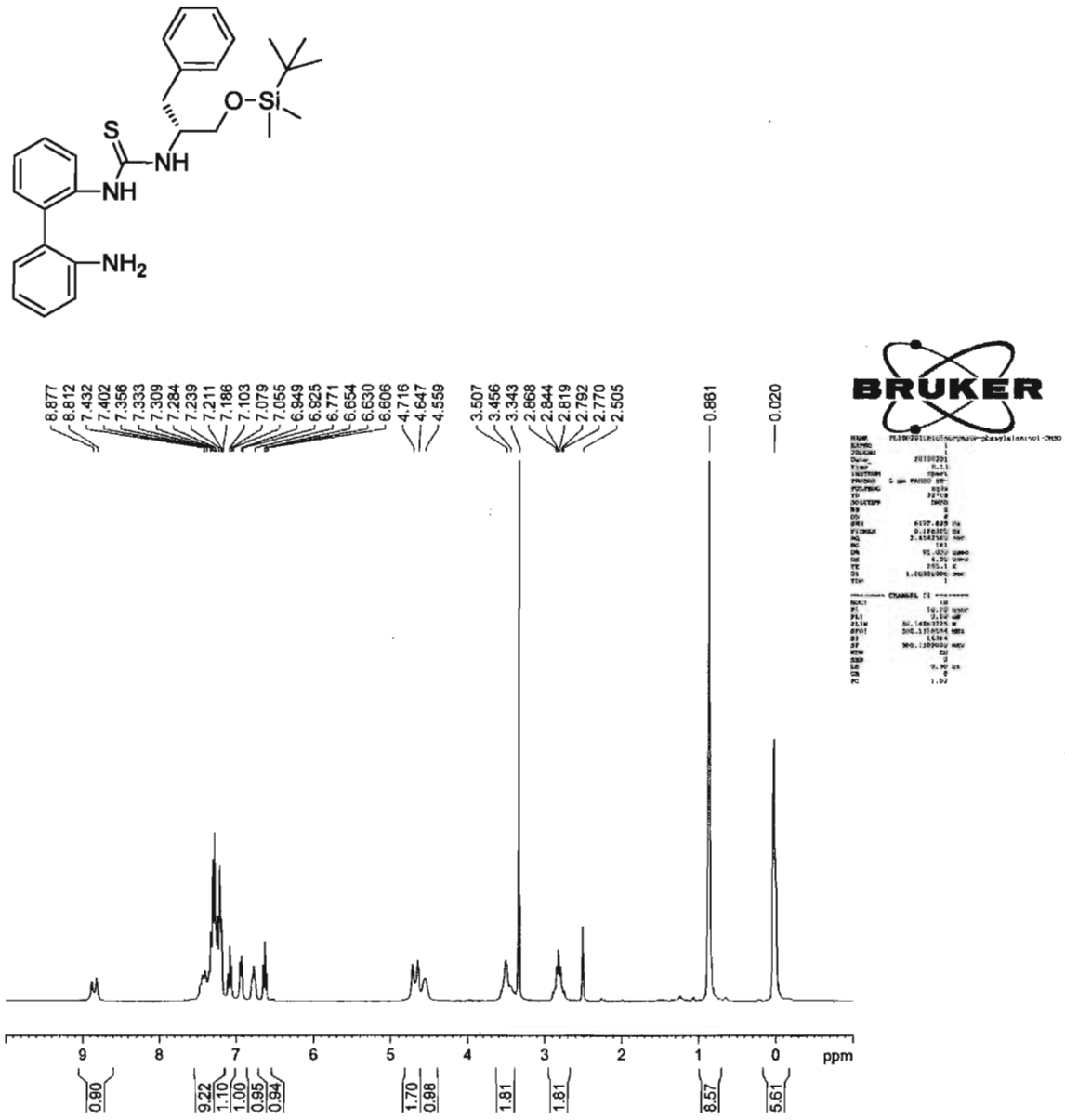


Figure IV-27: (*R*)-1-(2'-amino-[1,1'-biphenyl]-2-yl)-3-(1-((tert-butyldimethylsilyl)oxy)-3-phenylpropan-2-yl)thiourea ^{1}H-NMR (300MHz, DMSO).

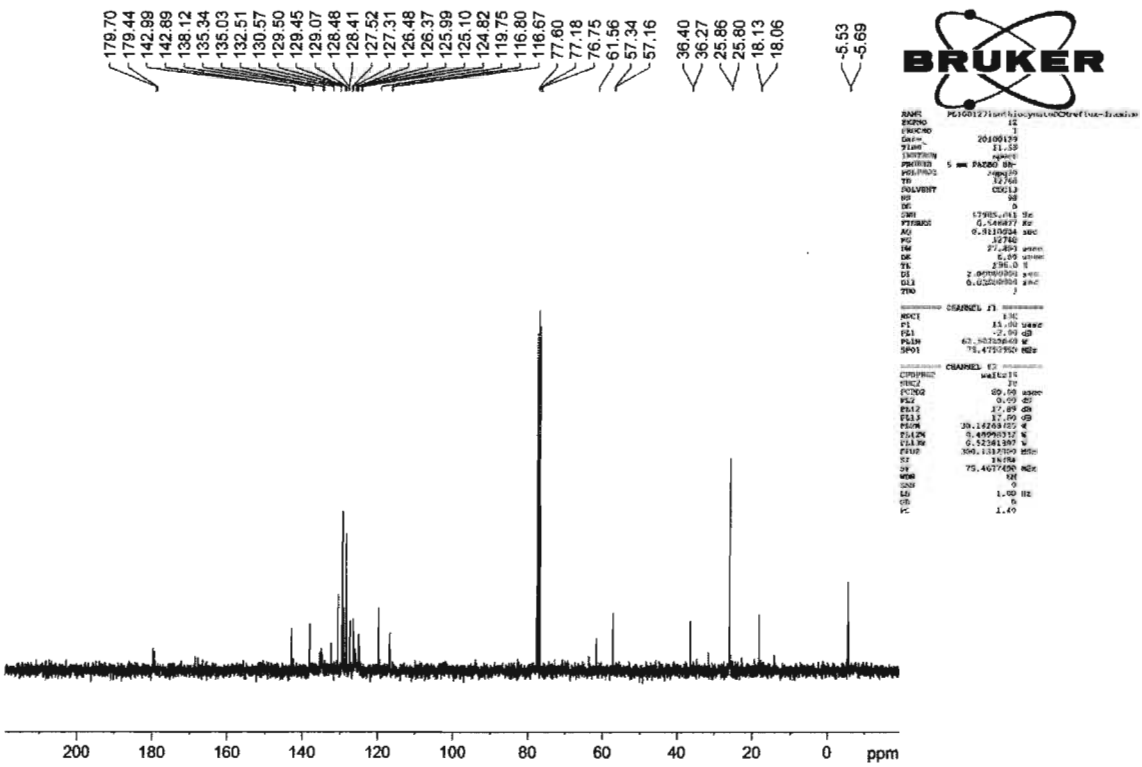


Figure IV-28: (*R*)-1-(2'-amino-[1,1'-biphenyl]-2-yl)-3-(1-((tert-butyldimethylsilyl)oxy)-3-phenylpropan-2-yl)thiourea ^{13}C-NMR (300MHz, $CDCl_3$). Double peaks are indicative of rotamers.

IV-1.16. (*R*)-1-((tert-butyldimethylsilyl)oxy)-N-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3-phenylpropan-2-amine (28)

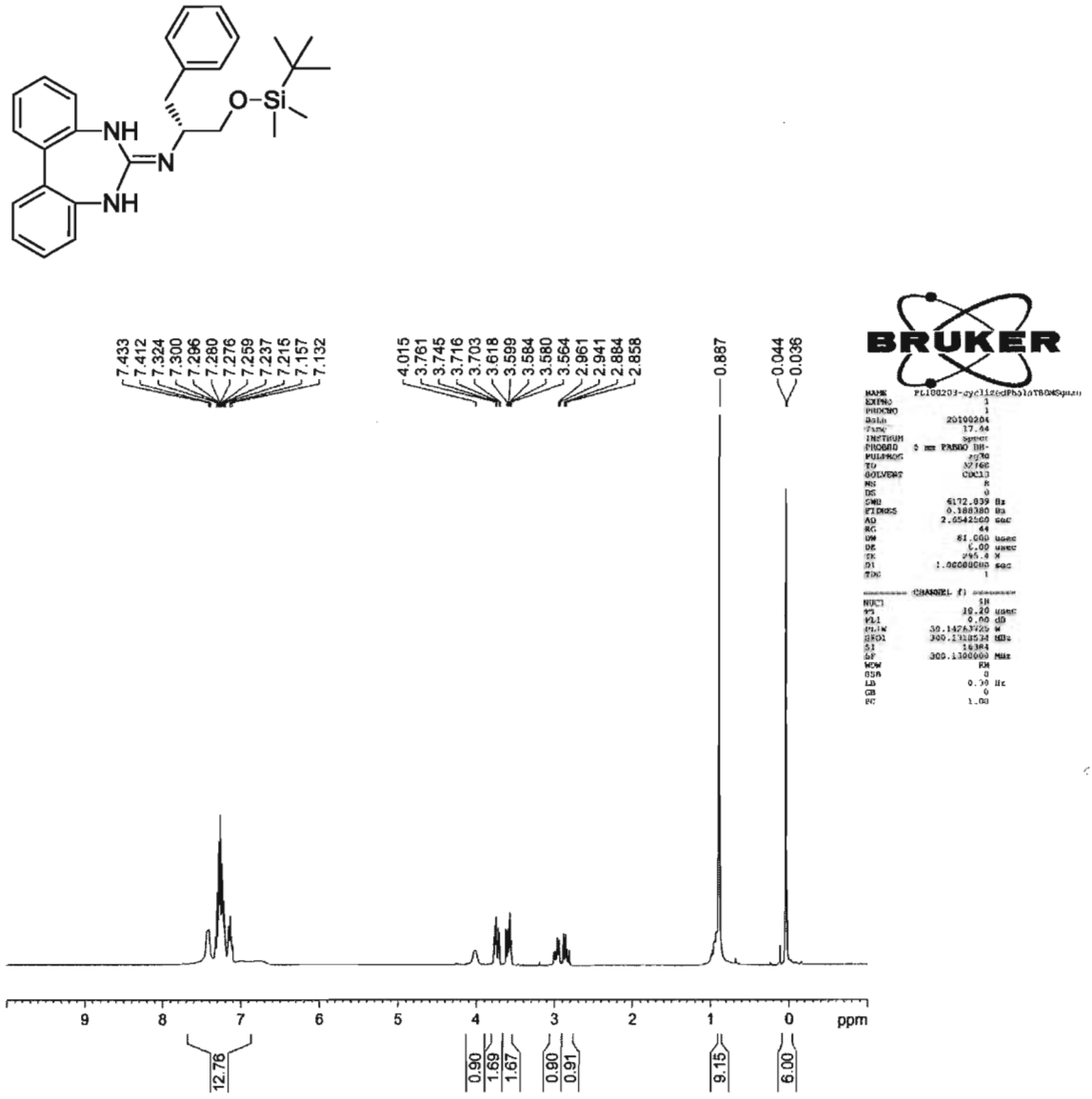
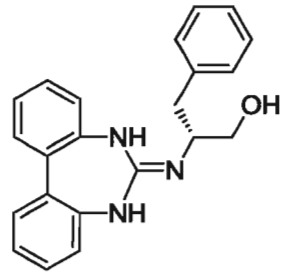
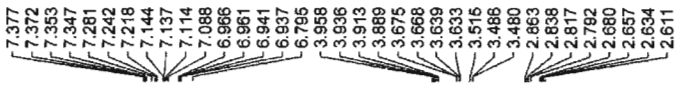


Figure IV-29: (*R*)-1-((tert-butyldimethylsilyl)oxy)-N-(5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)-3-phenylpropan-2-amine ^{1}H-NMR (300MHz, $CDCl_3$).

IV-1.17. (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol (29)





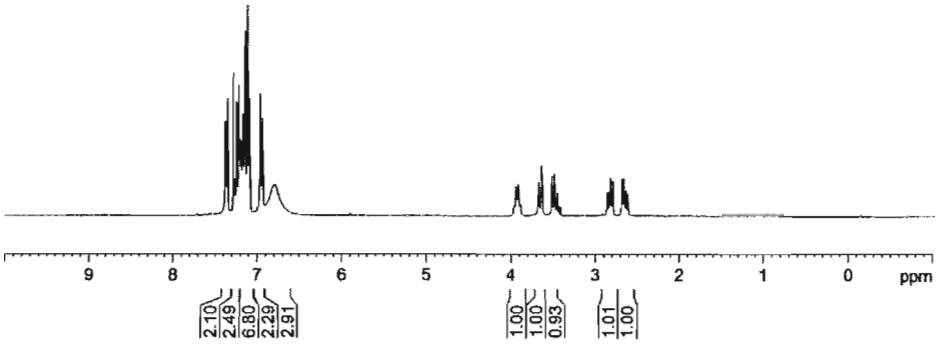


Figure IV-30: (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol ^{1}H-NMR (300MHz, $CDCl_3$).

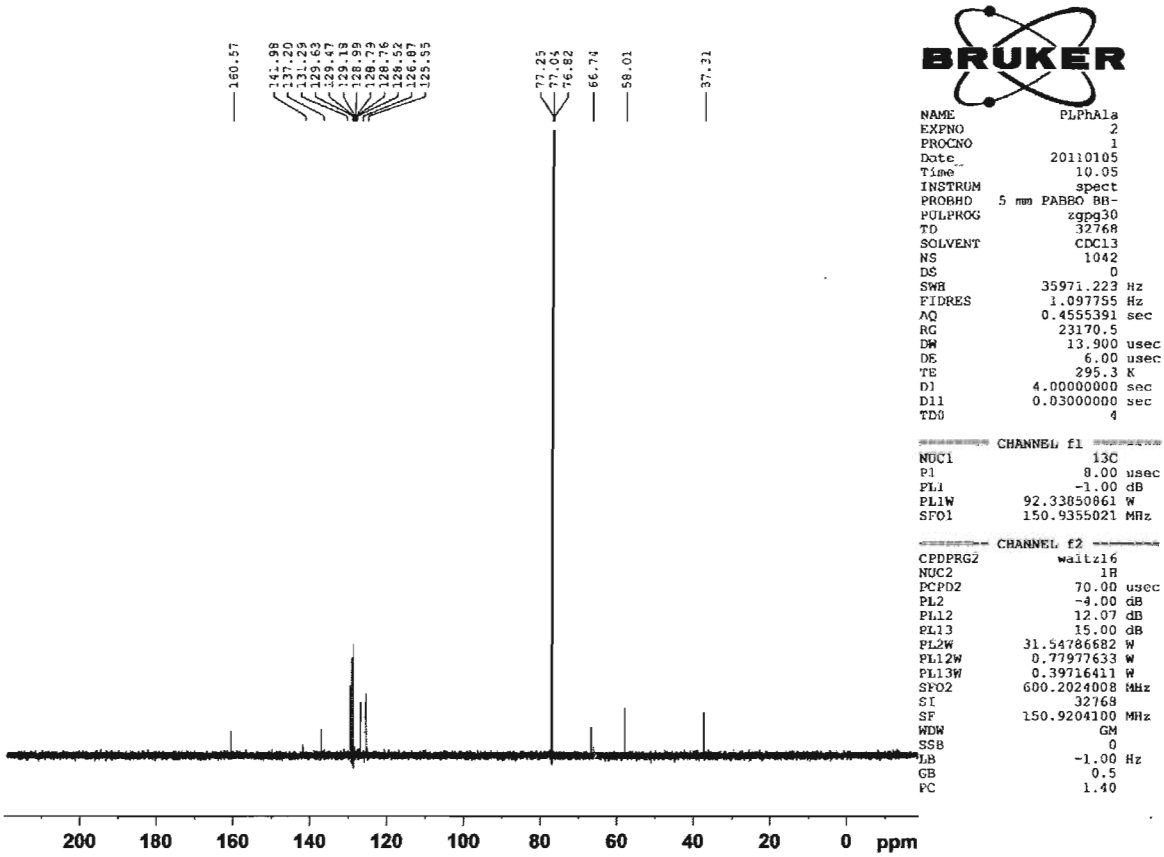
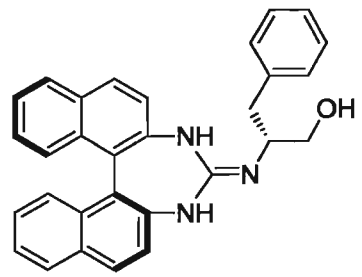
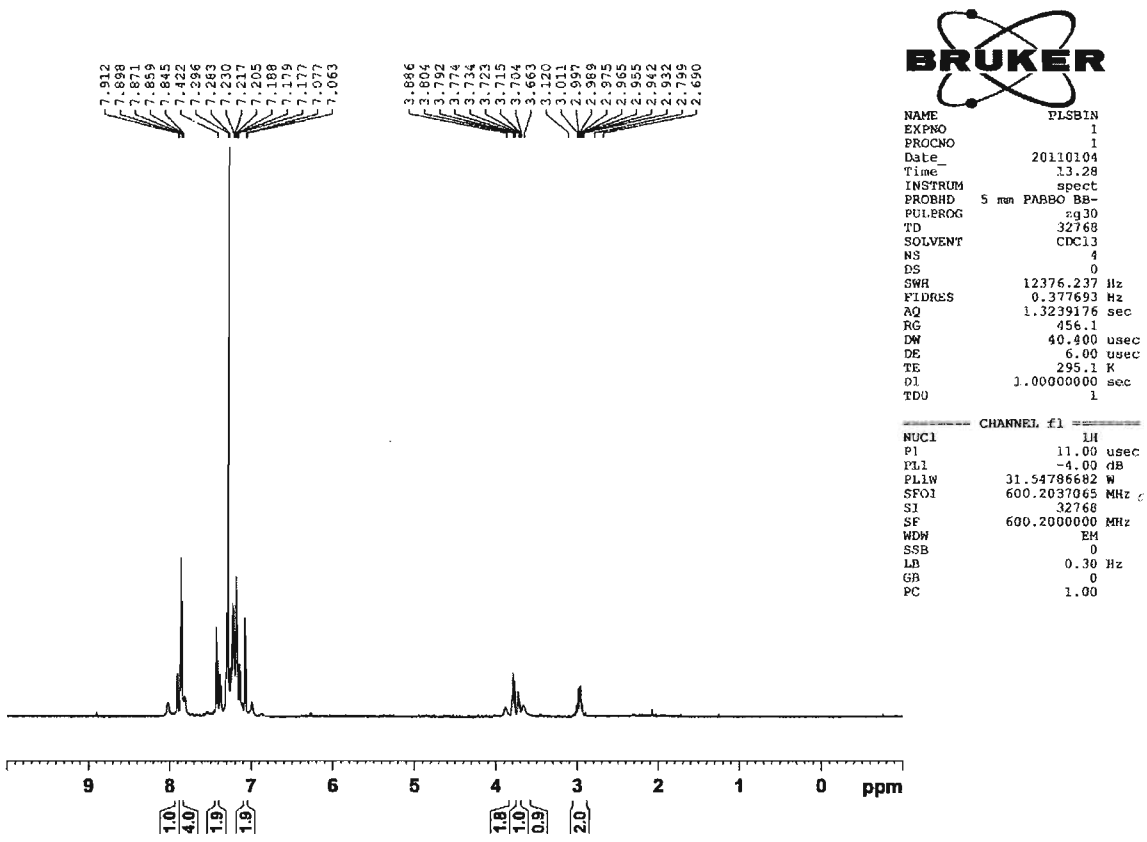


Figure IV-31: (*R*)-2-((5H-dibenzo[d,f][1,3]diazepin-6(7H)-ylidene)amino)-3-phenylpropan-1-ol ^{13}C-NMR (300MHz, $CDCl_3$).

IV-1.18. (*R*)-2-((Z)-((S)-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)amino)-3-phenylpropan-1-ol (31)





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PROCNO	1
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SOLVENT	CDCl3
NS	4
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SWH	12376.237 Hz
FIDRES	0.377693 Hz
AQ	1.3239176 sec
RG	456.1
DW	40.400 usec
DE	6.00 usec
TE	295.1 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	11.00 usec
PL1	-4.00 dB
PL1W	31.54786682 W
SFO1	600.2037065 MHz
SI	32768
SF	600.2000000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Figure IV-32: (*R*)-2-((Z)-((S)-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)amino)-3-phenylpropan-1-ol ^{1}H-NMR (600MHz, $CDCl_3$).

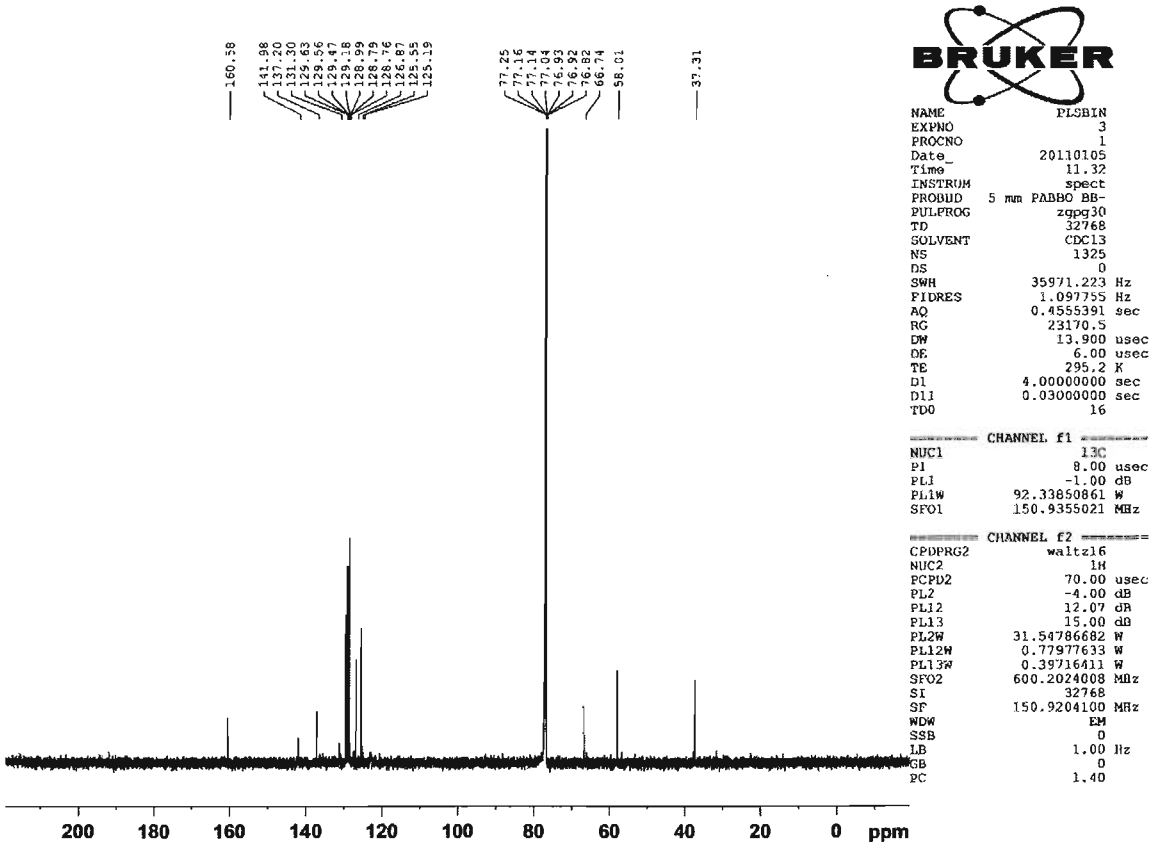


Figure IV-33: (*R*)-2-((Z)-((S)-3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)amino)-3-phenylpropan-1-ol ^{13}C-NMR (600MHz, $CDCl_3$).

IV-1.19. (2*R*)-2-((*Z*)-(3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)amino)-3-phenylpropan-1-ol (33)

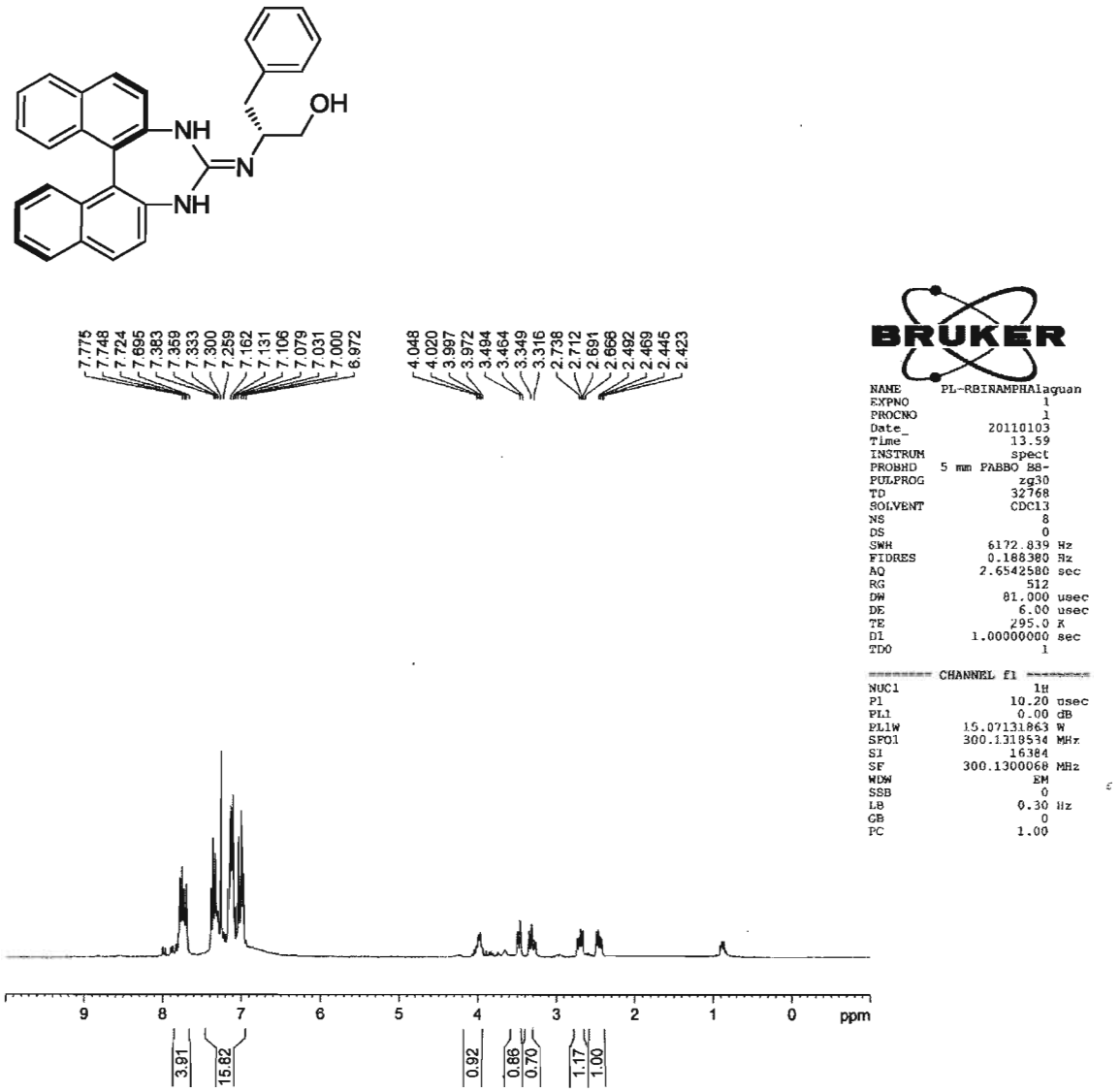


Figure IV-34: (2*R*)-2-((*Z*)-(3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)amino)-3-phenylpropan-1-ol ^{1}H-NMR (300MHz, $CDCl_3$).

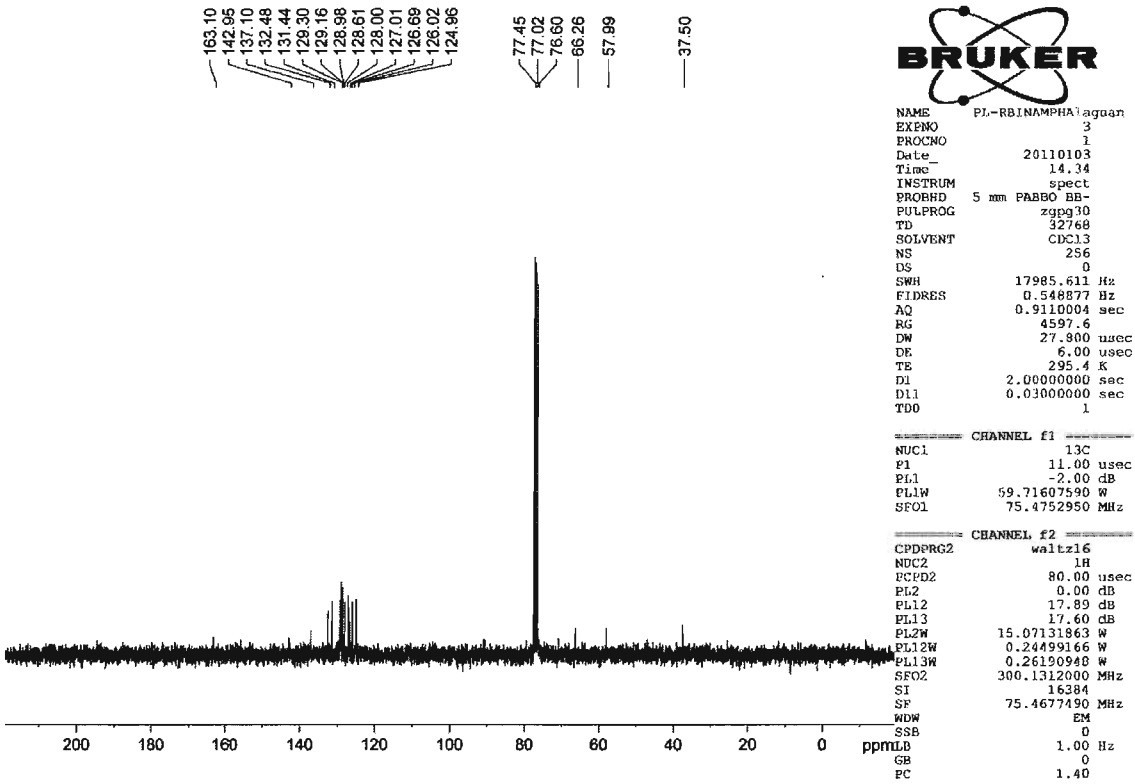
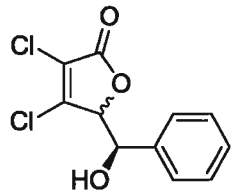


Figure IV-35: (2*R*)-2-((*Z*)-(3H-dinaphtho[2,1-d:1',2'-f][1,3]diazepin-4(5H)-ylidene)amino)-3-phenylpropan-1-ol ^{13}C-NMR (300MHz, $CDCl_3$).

IV-2. HPLC Information and Spectras for Vinylogous Aldol Adducts

IV-2.1. 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one



HPLC Analysis Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm) 17.4 (*anti*, major), 26.2 (*anti*), 17.1 (*syn*), 19.1 (*syn*, major); Using catalyst **29** *anti:syn* = 62:38; 35% ee (*anti*), 49% ee (*syn*) . Using catalyst **31** *anti:syn* = 60:40; 12% ee (*anti*), 16% ee (*syn*). Using catalyst **33** *anti:syn* = 60:40; 42% ee (*anti*), 62% ee (*syn*).

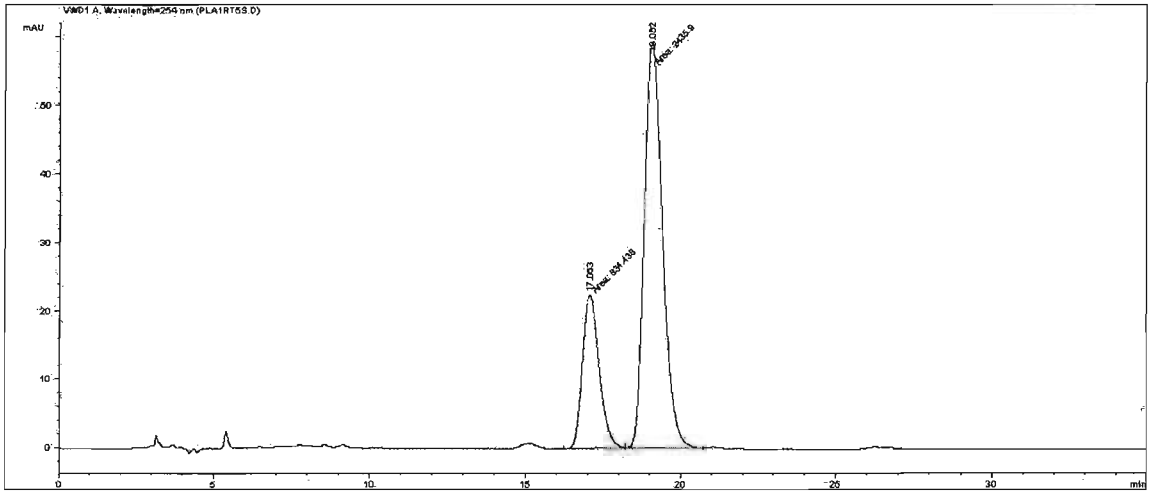


Figure IV-36: HPLC spectrum of *syn* isomer for 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 29.

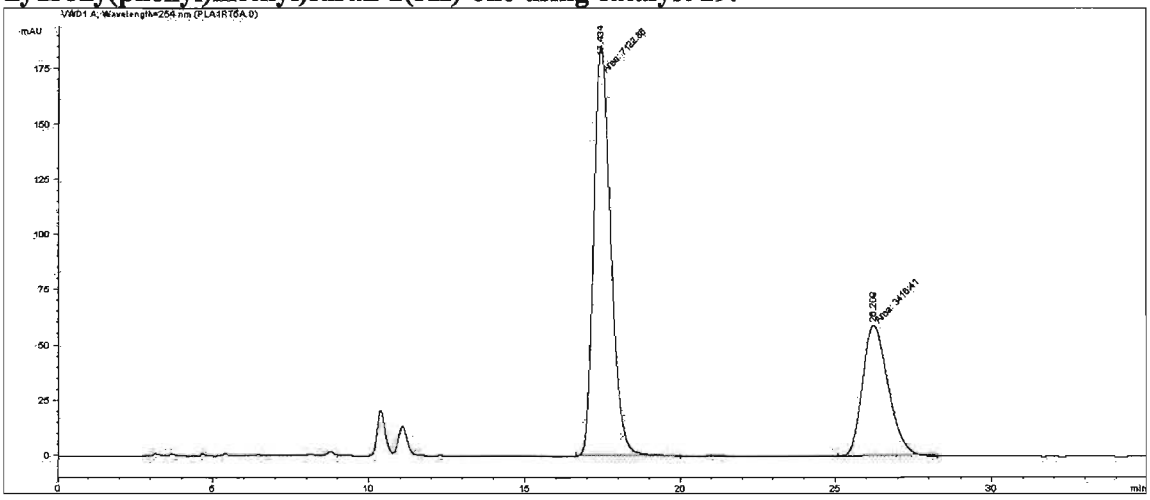


Figure IV-37: HPLC spectrum of *anti* isomer for 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 29.

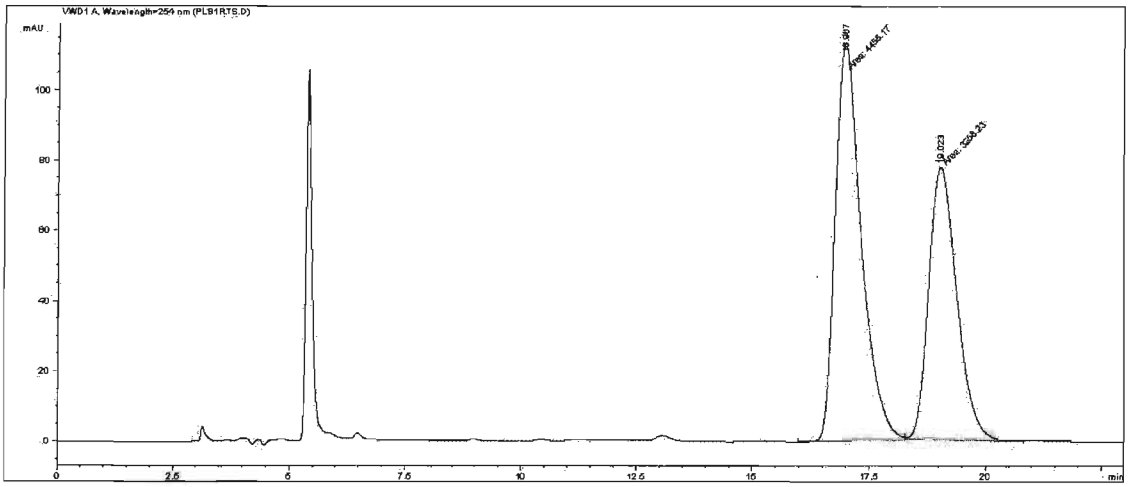


Figure IV-38: HPLC spectrum of *syn* isomer for 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 31.

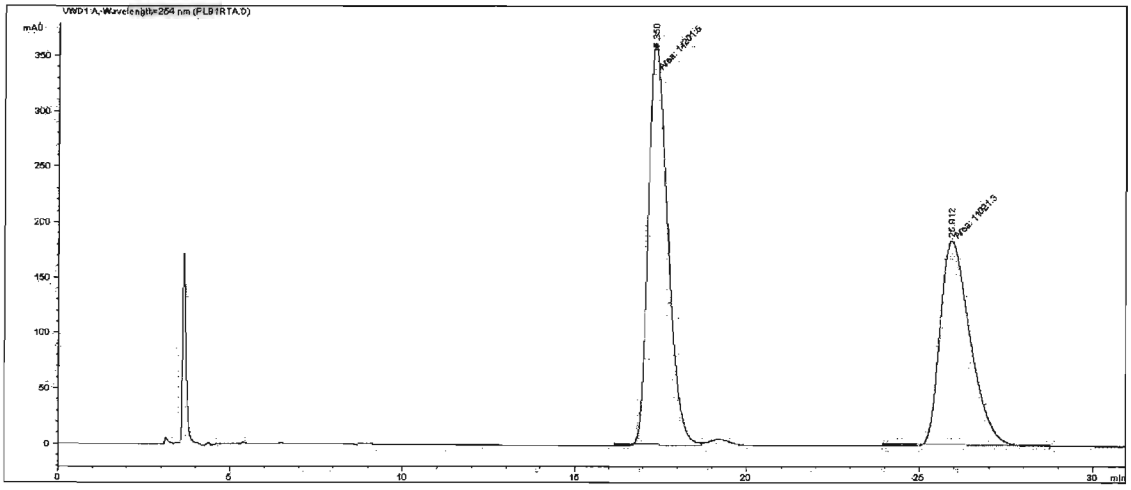


Figure IV-39: HPLC spectrum for *anti* isomer of 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 31.

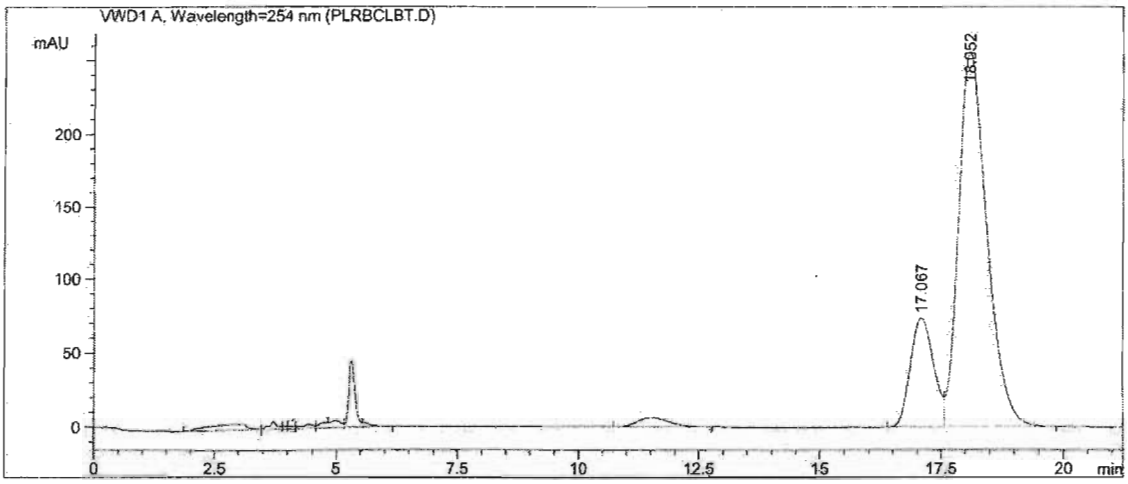


Figure IV-40: HPLC spectrum for syn isomer of 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 33.

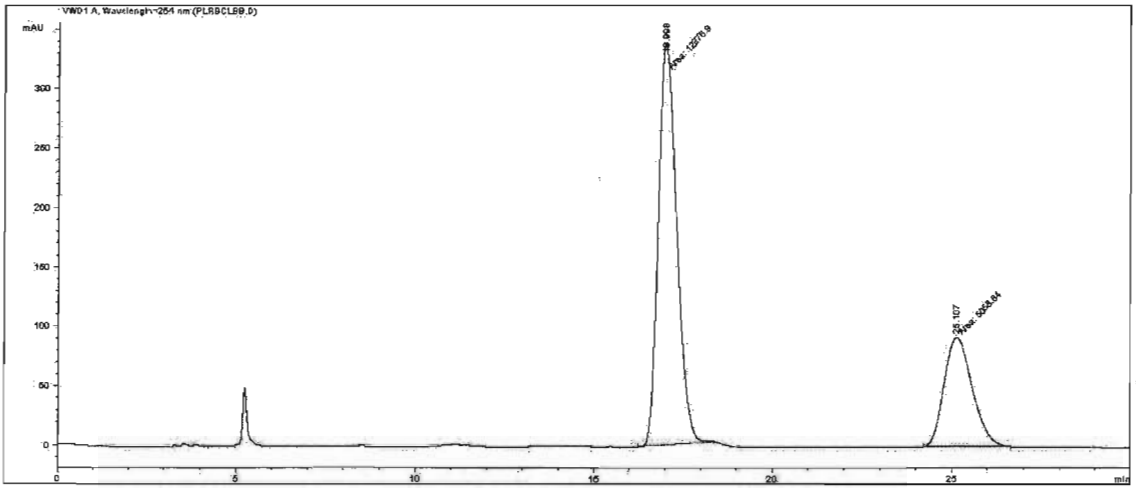
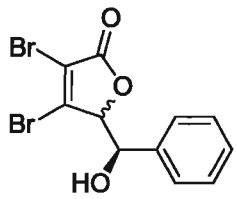


Figure IV-41: HPLC spectrum for *anti* isomer of 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 33.

IV-2.2. 3,4-dibromo-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one



HPLC Analysis: *anti* isomer Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); 20.1 (*anti*, major), 28.2 (*anti*). *Syn* isomer HPLC Analysis Chiralpak OD-H (hexane/IPA = 97/03, 1.2 mL/min, 254 nm); 17.1 (*syn*, major), 19.1 (*syn*). Using catalyst **29** *anti:syn* = 52:48; 37% ee (*anti*), 61% ee (*syn*). Using catalyst **33** *anti:syn* = 50:50; 44% ee (*anti*), 64% ee (*syn*).

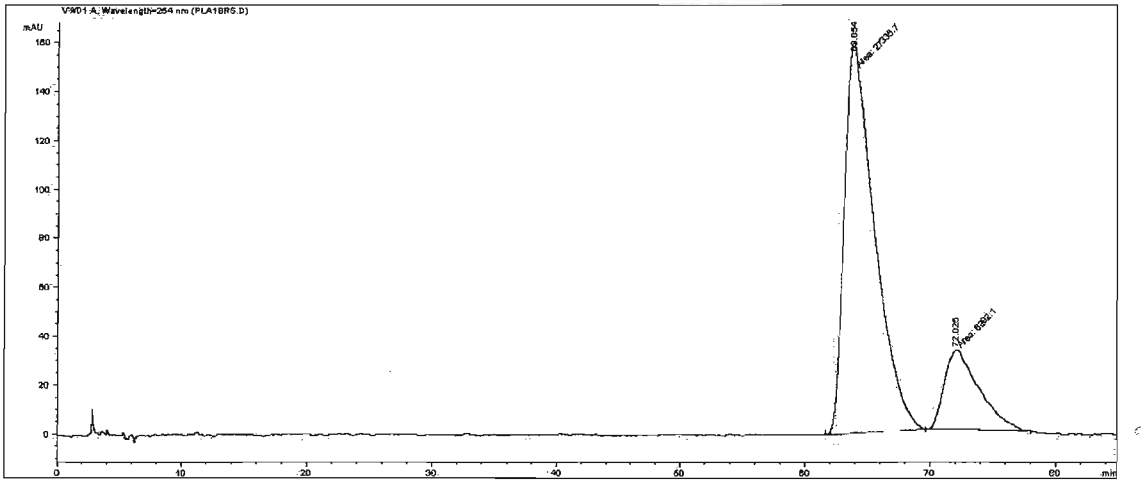


Figure IV-42: HPLC spectrum for *syn* isomer of 3,4-dibromo-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 29.

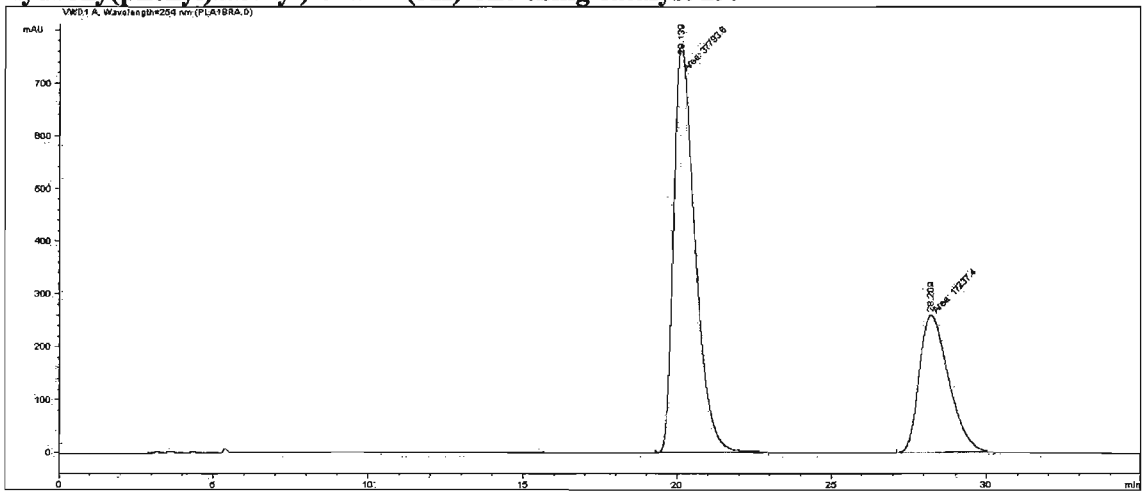


Figure IV-43: HPLC spectrum for *anti* isomer of 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 29.

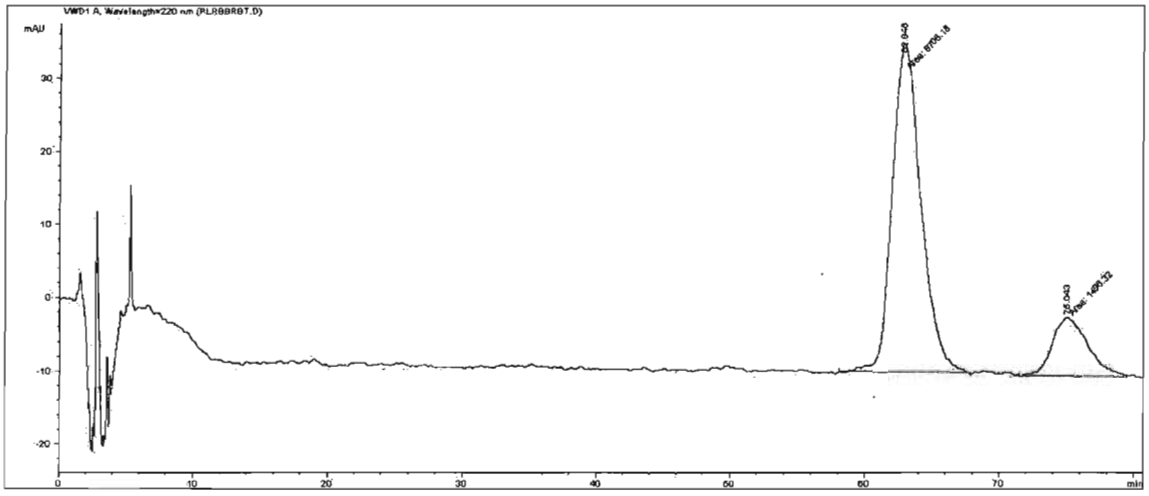


Figure IV-44: HPLC spectrum for *syn* isomer of 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 33.

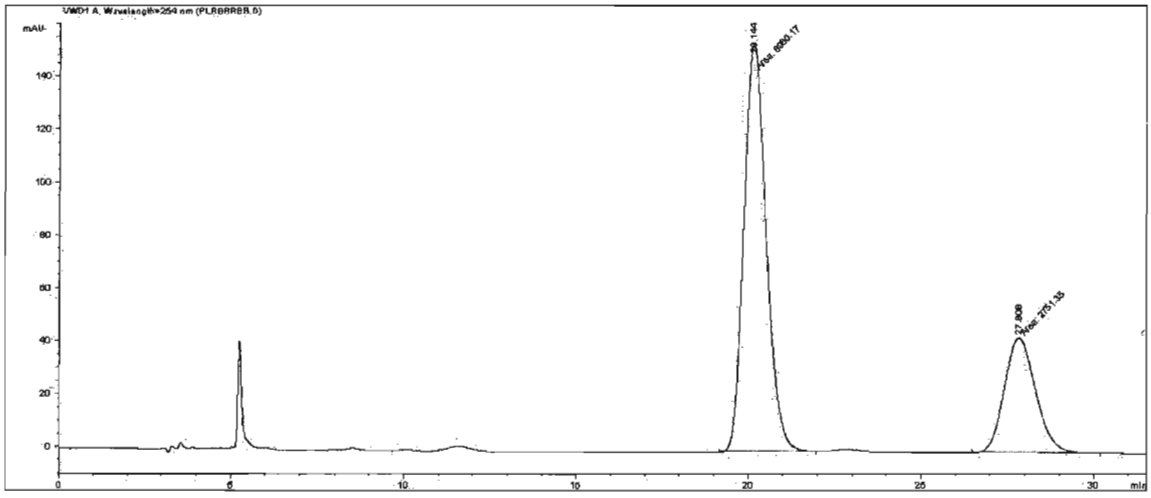
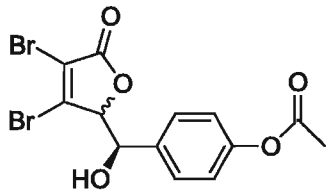


Figure IV-45: HPLC spectrum for *anti* isomer of 3,4-dichloro-5-((*R*)-hydroxy(phenyl)methyl)furan-2(5H)-one using catalyst 33.

IV-2.3. 4-((1*R*)-(3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)(hydroxy)methyl)phenyl acetate



HPLC Analysis Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); Using catalyst **29** *anti:syn* = 62:38; 28.3 (*anti*, major), 40.9 (*anti*), 28.6 (*syn*, major), 19.1 (*syn*); 17% ee (*anti*), 55% ee (*syn*).

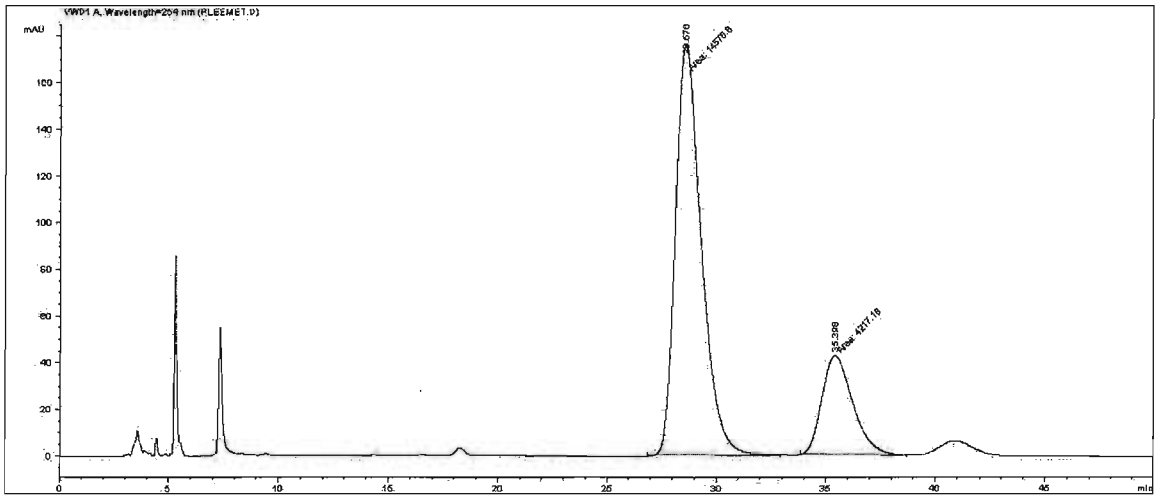


Figure IV-46: HPLC of *syn* isomer for 4-((1*R*)-(3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)(hydroxy)methyl)phenyl acetate.

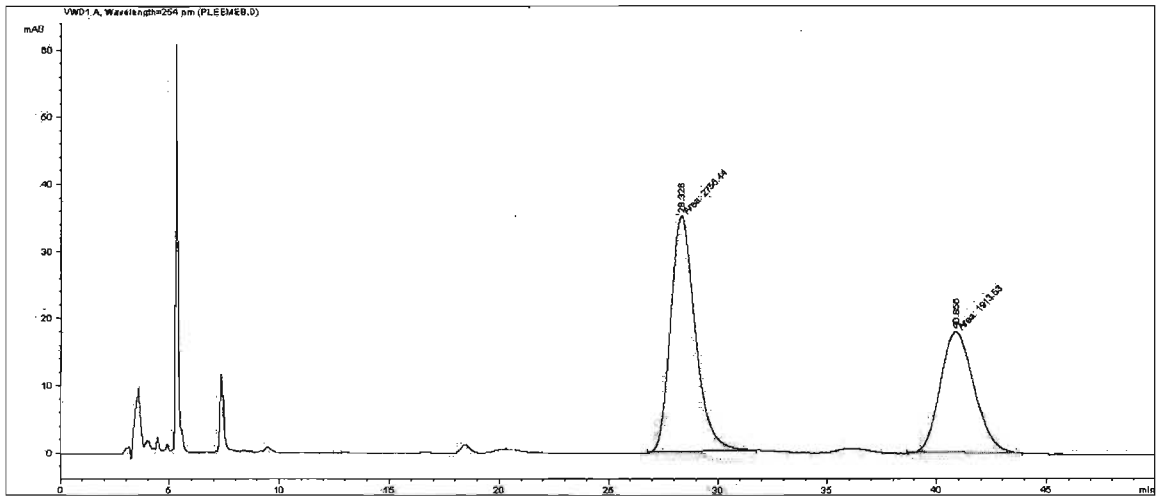
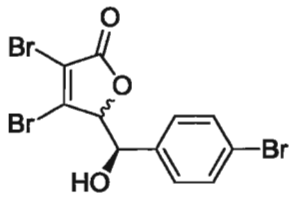


Figure IV-47: HPLC of *anti* isomer for 4-((1*R*)-(3,4-dibromo-5-oxo-2,5-dihydrofuran-2-yl)(hydroxy)methyl)phenyl acetate

IV-2.4. 3,4-dibromo-5-((*R*)-(4-bromophenyl)(hydroxy)methyl)furan-2(5H)-one



HPLC Analysis Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); Using catalyst **29** *anti:syn* = 53:47; 20.7 (*anti*, major), 29.5 (*anti*), 17.7 (*syn*, major), 25.2 (*syn*); 51% ee (*anti*), 51% ee (*syn*).

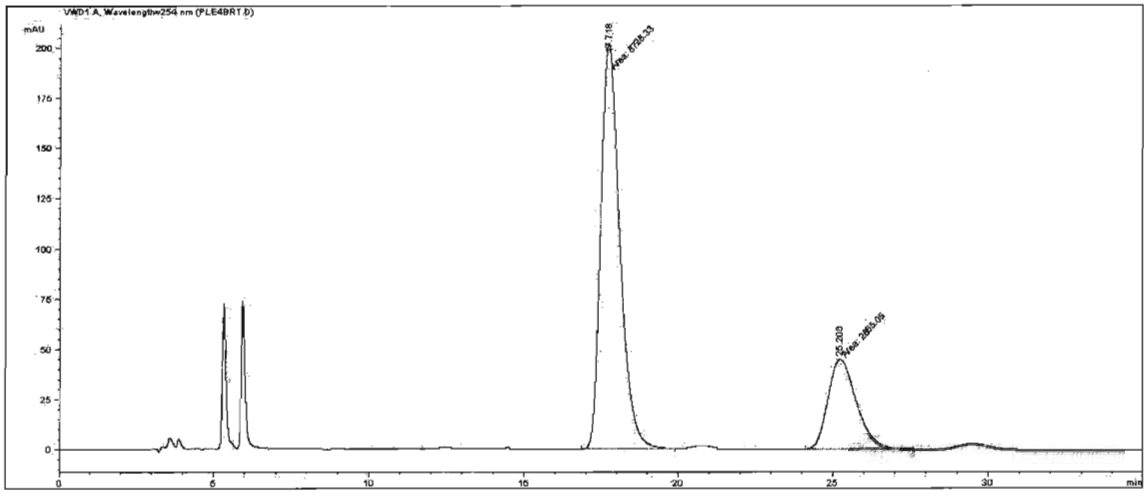


Figure IV-48: HPLC analysis for *syn* isomer of 3,4-dibromo-5-((*R*)-(4-bromophenyl)(hydroxy) methyl)furan-2(5H)-one.

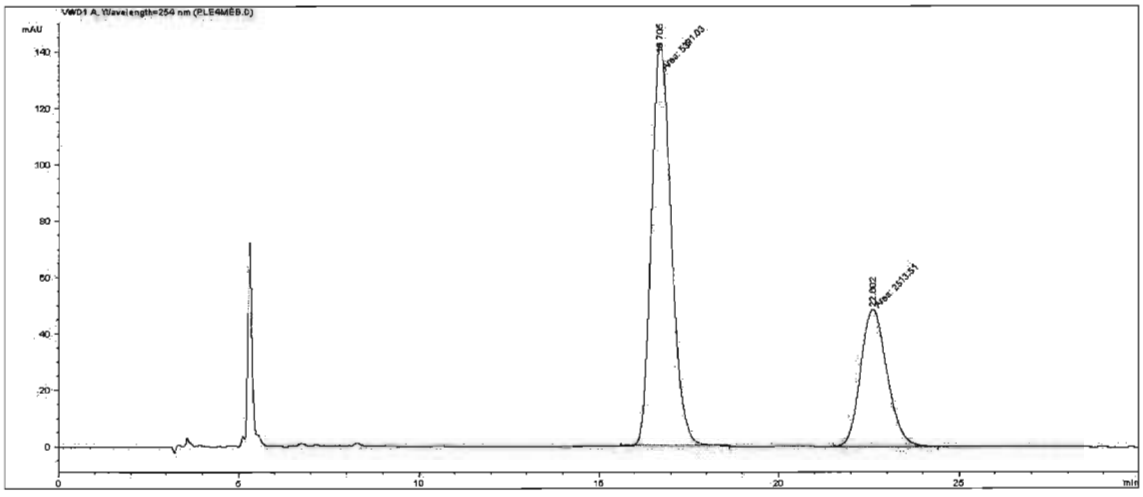
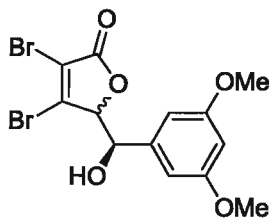


Figure IV-49: HPLC analysis for *anti* isomer of 3,4-dibromo-5-((*R*)-(4-bromophenyl)(hydroxy) methyl)furan-2(5H)-one.

IV-2.5. 3,4-dibromo-5-((*R*)-(3,5-dimethoxyphenyl)(hydroxy)methyl)furan-2(5H)-one



HPLC Analysis Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); Using catalyst **29** *anti:syn* = 55:45; 17.3 (*anti*), 23.0 (*anti*, major), 24.9 (*syn*, major), 37.8 (*syn*); 35% ee (*anti*), 65% ee (*syn*).

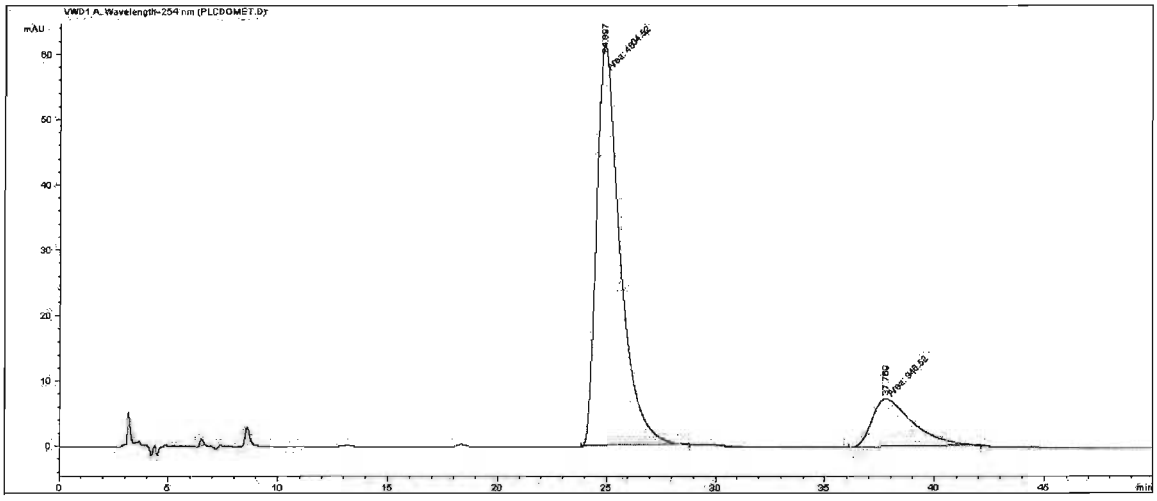


Figure IV-50: HPLC analysis for *syn* isomer of 3,4-dibromo-5-((*R*)-(3,5-dimethoxyphenyl)(hydroxy) methyl)furan-2(5H)-one.

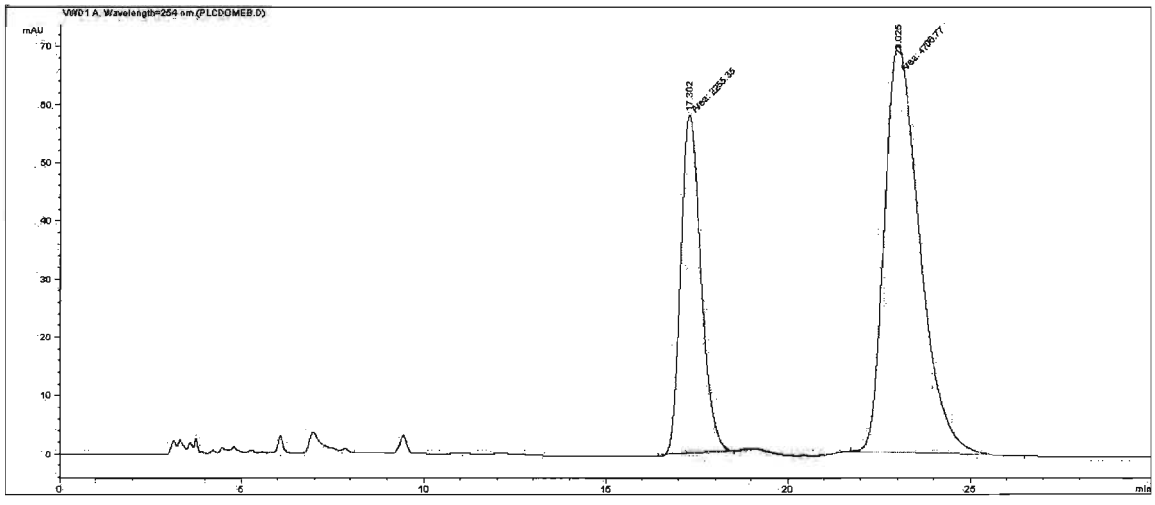
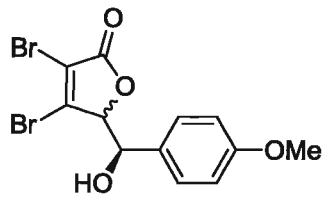


Figure IV-51: HPLC analysis for *anti* isomer of 3,4-dibromo-5-((*R*)-(3,5-dimethoxyphenyl)(hydroxy) methyl)furan-2(5H)-one.

IV-2.6. 3,4-dibromo-5-((*R*)-hydroxy(4-methoxyphenyl)methyl)furan-2(5H)-one



HPLC Analysis Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); Using catalyst **29** *anti:syn* = 51:49; 24.3 (*anti*, major), 28.7 (*anti*), 23.1 (*syn*, major), 28.2 (*syn*); 39% ee (*anti*), 55% ee (*syn*).

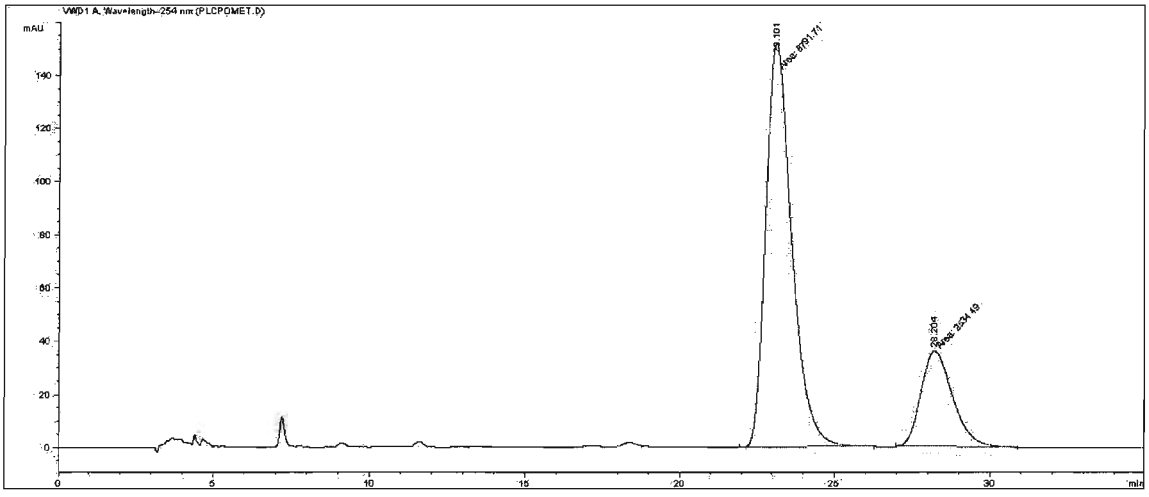


Figure IV-52: HPLC analysis for *syn* isomer of 3,4-dibromo-5-((*R*)-hydroxy(4-methoxyphenyl) methyl)furan-2(5H)-one.

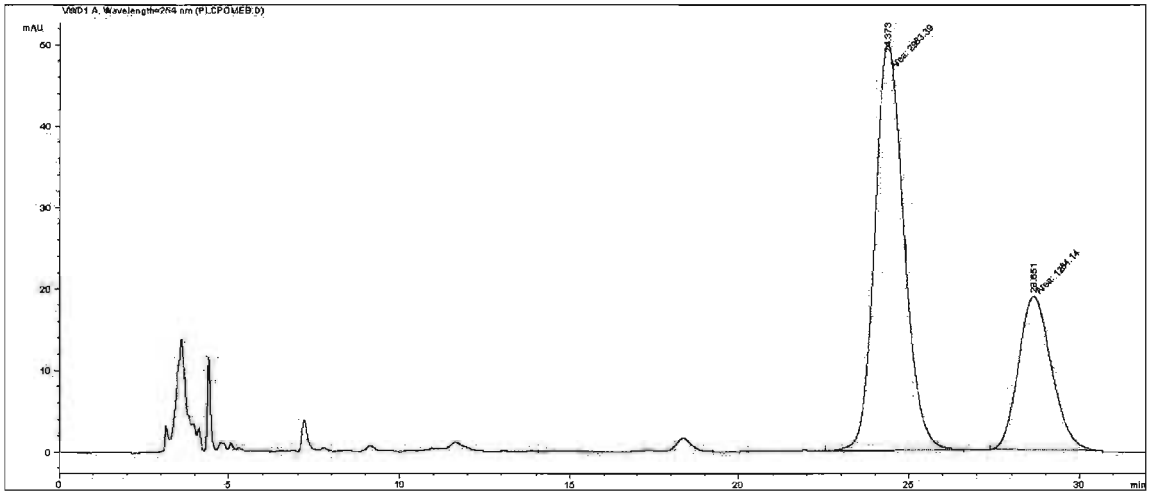
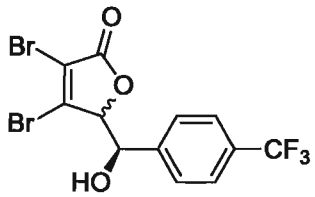


Figure IV-53: HPLC analysis for *anti* isomer of 3,4-dibromo-5-((*R*)-hydroxy(4-methoxyphenyl) methyl)furan-2(5H)-one.

IV-2.7. 3,4-dibromo-5-((*R*)-hydroxy(4-(trifluoromethyl)phenyl)methyl)furan-2(5H)-one



HPLC Analysis Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); Using catalyst **29** *anti:syn* = 46:54; 16.8 (*anti*, major), 26.1 (*anti*), 13.3 (*syn*, major), 19.3 (*syn*); 22% ee (*anti*),53% ee (*syn*).

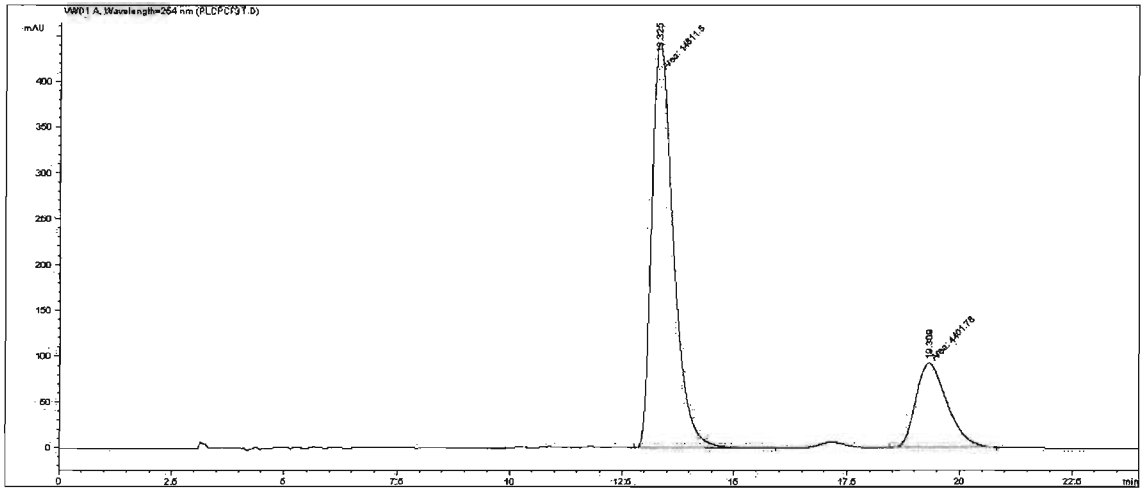


Figure IV-54: HPLC analysis for *syn* isomer of 3,4-dibromo-5-((*R*)-hydroxy(4-(trifluoromethyl)phenyl)methyl)furan-2(5H)-one.

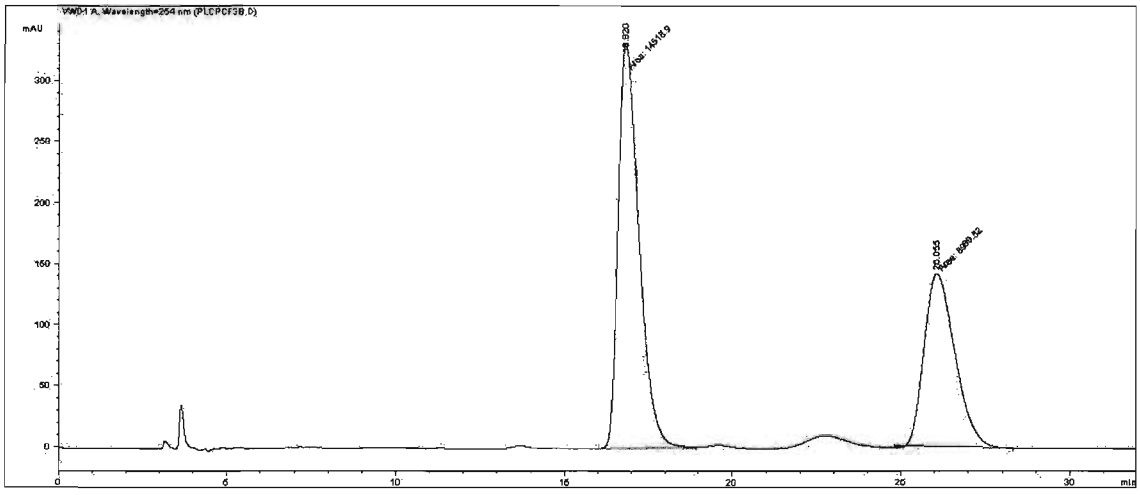
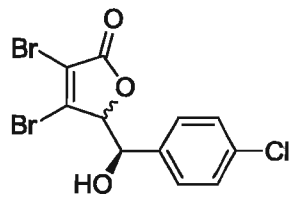


Figure IV-55: HPLC analysis for *anti* isomer of 3,4-dibromo-5-((*R*)-hydroxy(4-(trifluoromethyl)phenyl)methyl)furan-2(5H)-one.

IV-2.8. 3,4-dibromo-5-((*R*)-(4-chlorophenyl)(hydroxy)methyl)furan-2(5H)-one



HPLC Analysis Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); Using catalyst **29** *anti:syn* = 58:42; 16.2 (*anti*, major), 22.2 (*anti*), 14.5 (*syn*, major), 18.5 (*syn*, major); 54% ee (*anti*), 96% ee (*syn*).

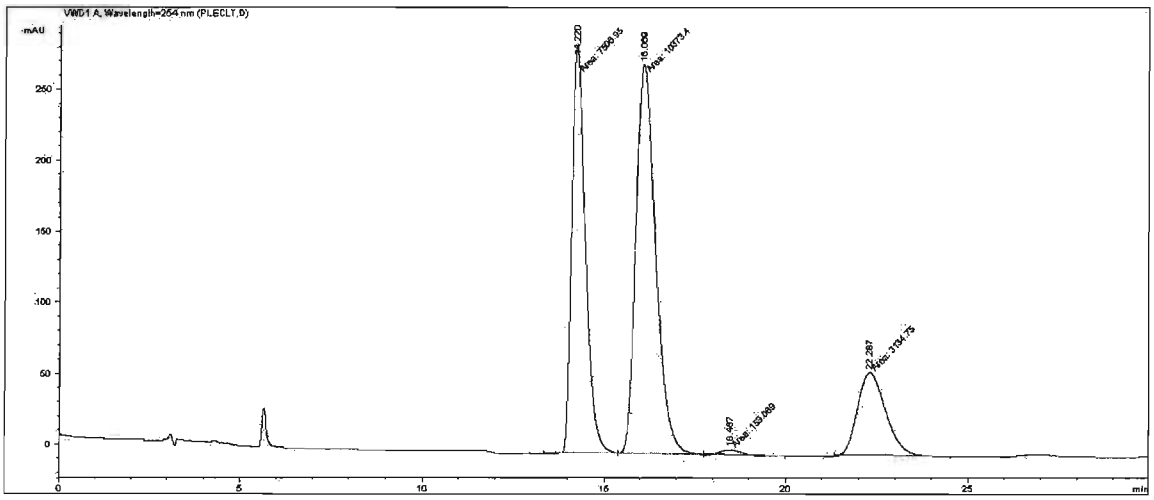
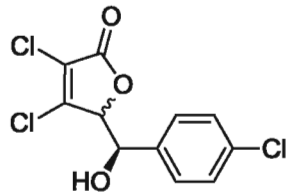


Figure IV-56: HPLC analysis for *syn/anti* isomers of 3,4-dibromo-5-((*R*)-(4-chlorophenyl)(hydroxy) methyl)furan-2(5H)-one.

IV-2.9. 3,4-dichloro-5-((*R*)-(4-chlorophenyl)(hydroxy)methyl)furan-2(5H)-one



HPLC Analysis: *anti* isomer: Chiralpak OD-H (hexane/IPA = 90/10, 1mL/min, 254 nm); Using catalyst **29** *anti:syn* = 48:52; 14.3 (*anti*, major), 17.7 (*anti*); 16% ee. *Syn* isomer: Chiralpak OD-H (hexane/IPA = 95/5, 0.5mL/min, 254nm); 57.3 (*syn*, major), 64.6 (*syn*); 20% ee (syn).

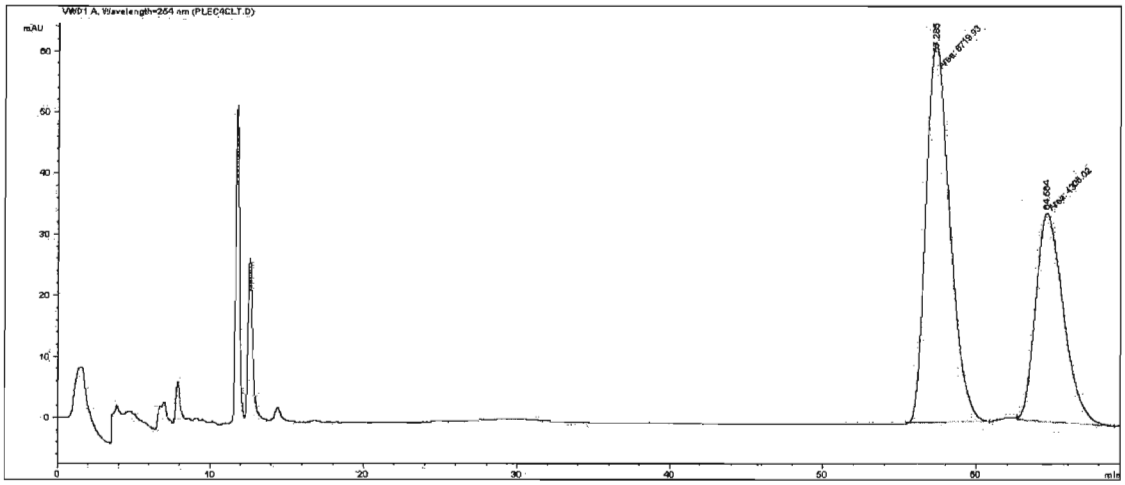


Figure IV-57: HPLC analysis for *syn* isomers of 3,4-dichloro-5-((*R*)-(4-chlorophenyl)(hydroxy) methyl)furan-2(5H)-one.

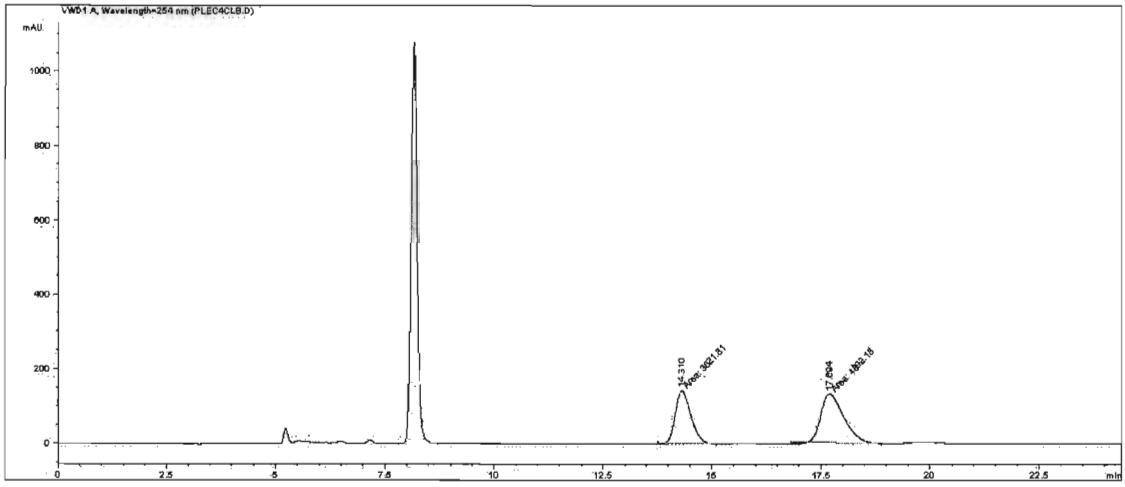


Figure IV-58: HPLC analysis for *anti* isomers of 3,4-dichloro-5-((*R*)-(4-chlorophenyl)(hydroxy) methyl)furan-2(5H)-one.